IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ORION CORPORATION, Plaintiff, v. WOCKHARDT USA, INC., and WOCKHARDT LIMITED, Defendants.	CIVIL ACTION NO.

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff, Orion Corporation (hereinafter "Orion"), brings this action for patent infringement against Wockhardt USA, Inc. and Wockhardt Limited (hereinafter collectively "Defendants"). This action concerns two patents relating to the pharmaceutical entacapone, Comtan®, a prescription drug used in the treatment of Parkinson's Disease as an adjunct to levodopa/carbidopa therapy.

JURISDICTION AND PARTIES

1. Plaintiff Orion is a Finnish company having an office and principal place of business at Orionintie 1, FI-02200 Espoo, Finland. Orion is engaged in the business of research, development, and sale of pharmaceutical products throughout the world.

2. Upon information and belief, Wockhardt Limited (hereinafter "Wockhardt") is an Indian company and maintains an office at Bandra (East), Mumbai, Maharashtra 400 051, India.

3. Upon information and belief, Wockhardt USA, Inc. (hereinafter "Wockhardt USA") is a Delaware corporation and is a wholly-owned subsidiary of Wockhardt. The website for Wockhardt USA lists an office at 75 Ronald Reagan Boulevard, Warwick, New York 10990.

4. Upon information and belief, Wockhardt manufactures generic pharmaceuticals and markets them throughout the United States through its wholly-owned and directly-controlled subsidiary Wockhardt USA.

5. Personal jurisdiction over Wockhardt is proper because Wockhardt has consented to personal jurisdiction for the purpose of this litigation in this Court.

6. Personal jurisdiction over Wockhardt USA is proper because Wockhardt USA has consented to personal jurisdiction for the purpose of this litigation in this Court.

7. This action for patent infringement arises under the United States Patent Laws, Title 35, United States Code, including 35 U.S.C. §§ 271 (a), (b), (c), and (e), and §§ 281-285. Subject matter jurisdiction is proper under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202. Venue is proper in this judicial district because both Wockhardt and Wockhardt USA have agreed to venue in this Court for the purpose of this litigation.

BACKGROUND

8. United States Patent No. 5,446,194 ("the '194 patent") for PHARMACOLOGICALLY ACTIVE CATECHOL DERIVATIVES was duly and legally issued to Orion-yhtymä Oy by the United States Patent and Trademark Office on August 29, 1995. The '194 patent is presently owned by Orion. A copy of the '194 patent is attached hereto as Exhibit A.

9. United States Patent No. 5,135,950 ("the '950 patent") for STABLE POLYMORPHIC FORM OF (E)-N,N-DIETHYL-2-CYANO-3-(3,4-DIHY-DROXY-5-NITROPHENYL)ACRYLAMIDE AND THE PROCESS FOR ITS PREPARATION was duly and legally issued to Orion-yhtymä Oy by the United States Patent and Trademark Office on August 4, 1992. The '950 patent is presently owned by Orion. A copy of the '950 patent is attached hereto as Exhibit B.

10. Orion is the holder of a New Drug Application approved by the United States Food and Drug Administration ("FDA") for the use of entacapone in the treatment of Parkinson's Disease as an adjunct to levodopa/carbidopa therapy.

11. Orion, through its partner Novartis, sells Comtan®, an entacapone-based product approved by the FDA for use in the treatment of Parkinson's disease, in the United States.

12. Upon information and belief, Wockhardt, through its agent, Wockhardt USA, has filed with the FDA, in Rockville, Maryland, an Abbreviated New Drug Application

("ANDA") under 21 U.S.C. § 355(j) to obtain approval for the commercial manufacture, use, importation, and sale of entacapone 200 mg tablets for the treatment of Parkinson's disease. Upon information and belief, Wockhardt filed the ANDA, assigned ANDA number 78-941, to obtain approval to market a generic version of entacapone before the expiration of the '194 or the '950 patents.

13. Upon information and belief, Wockhardt also filed with the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging, *inter alia*, that the claims of the '194 and '950 patents are either invalid, unenforceable, or not infringed.

14. Counsel for Wockhardt sent a letter dated August 3, 2007, to Orion to notify Orion that Wockhardt had filed an ANDA for entacapone 200 mg tablets and was providing Orion with information pursuant to 355(j)(2)(B)(ii). Orion received the letter on or about August 6, 2007.

15. Upon information and belief, Wockhardt's package insert will have the same indications and dosage instructions as those contained in the FDA-approved Comtan® tablet product package insert.

COUNT I

PATENT INFRINGEMENT OF THE '194 PATENT

16. Paragraphs 1-15 are incorporated herein by reference.

17. Under 35 U.S.C. § 271(e)(2)(A), Defendants infringed one or more claims of the '194 patent by submitting to the FDA an ANDA seeking approval for the commercial marketing, before the expiration date of the '194 patent, of entacapone 200 mg tablets, a product the manufacture, importation, use, or sale of which would infringe one or more claims of the '194 patent.

18. Orion will be substantially and irreparably damaged and harmed if Defendants' infringement is not enjoined. Orion does not have an adequate remedy at law.

COUNT II

PATENT INFRINGEMENT OF THE '950 PATENT

19. Paragraphs 1-15 are incorporated herein by reference.

20. Under 35 U.S.C. § 271(e)(2)(A), Defendants infringed one or more claims of the '950 patent by submitting to the FDA an ANDA seeking approval for the commercial marketing, before the expiration date of the '950 patent, of entacapone 200 mg tablets, a product the manufacture, importation, use or sale of which would infringe one or more claims of the '950 patent.

21. Upon information and belief, Defendants will also induce or contribute to infringement of one or more claims of the '950 patent by actively aiding, abetting, encouraging, and inducing, upon FDA approval, the sale of such an entacapone tablet product together with instructions and labeling which will result in direct infringement of one or more claims of the '950 patent by ultimate purchasers.

22. Orion will be substantially and irreparably damaged and harmed if Defendants' infringement is not enjoined. Orion does not have an adequate remedy at law.

COUNT III

DECLARATORY JUDGMENT IN FAVOR OF THE '194 PATENT

23. Paragraphs 1-22 are incorporated herein by reference.

24. Upon information and belief, Defendants have made substantial preparations to sell entacapone 200 mg tablets labeled for the same indications and the same dosage and method of use as the Comtan® product sold by Orion.

25. Upon further information and belief, Defendants further intend to commence sales of such entacapone 200 mg tablets immediately upon receiving approval from the FDA.

26. The manufacture, importation, sale, and offer for sale of entacapone 200 mg tablets so labeled, once approved by the FDA, will directly infringe, induce and/or contribute to infringement of one or more claims of the '194 patent under 35 U.S.C. § 271 (a), (b), and/or (c).

27. Orion will be substantially and irreparably damaged and harmed if Defendants' threatened infringement is not enjoined. Orion does not have an adequate remedy at law.

COUNT IV

DECLARATORY JUDGMENT IN FAVOR OF THE '950 PATENT

28. Paragraphs 1-22 are incorporated herein by reference.

29. Upon information and belief, Defendants have made substantial preparations to sell entacapone 200 mg tablets labeled for the same indications and the same dosage and method of use as the Comtan® product sold by Orion.

30. Upon further information and belief, Defendants further intend to commence sales of such entacapone 200 mg tablets immediately upon receiving approval from the FDA.

31. The manufacture, importation, sale, and offer for sale of entacapone 200 mg tablets so labeled, once approved by the FDA, will directly infringe, induce and/or contribute to infringement of one or more claims of the '950 patent under 35 U.S.C. § 271(a), (b), and/or (c).

32. Orion will be substantially and irreparably damaged and harmed if Defendants' threatened infringement is not enjoined. Orion does not have an adequate remedy at law.

COUNT V

EXCEPTIONAL CASE

33. Paragraphs 1-32 are incorporated herein by reference.

34. Defendants have proceeded with their unlawful activities despite knowledge of the '194 and '950 patents under 35 U.S.C. § 284.

35. This is an exceptional case warranting imposition of attorney fees against Defendants under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Orion respectfully requests this Court to enter judgment against Defendants as follows:

(a) finding that Defendants have infringed one or more claims of the '194 or '950 patents by filing the aforesaid ANDA relating to Wockhardt's entacapone 200 mg tablets;

(b) prohibiting any approval by the FDA of Defendants' aforesaid entacapone 200 mg tablets on any effective date prior to the date of expiration of the latest to expire of the '194 or '950 patents, or such later date as the Court may determine;

(c) declaring that Defendants will infringe one or more claims of the '194 or '950 patents if Wockhardt's aforesaid ANDA relating to entacapone 200 mg tablets is approved and the approved product is sold and used in the United States;

(d) enjoining Defendants, their officers, agents, attorneys, and employees, and those acting in privity or concert with them or any of them, from the commercial manufacture, use, importation, or sale of an entacapone 200 mg tablet product labeled for use in treating Parkinson's disease until the expiration of the '194 and '950 patents.

(e) finding that this is an exceptional case and granting Orion reasonable attorney fees pursuant to 35 U.S.C. § 285; and

(f) awarding Orion any further and additional relief as this Court deems just and proper.

Dated: September 13, 2007

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EXHIBIT A

US005446194A

United States Patent [19]

Bäckström et al.

[11] Patent Number: 5,446,194

[45] Date of Patent: Aug. 29, 1995

[54] **PHARMACOLOGICALLY ACTIVE CATECHOL DERIVATIVES**

[75] Inventors: **Reijo J. Bäckström,** Helsinki; **Kalevi E. Heinola,** Järvempää ; **Erkki J. Honkanen,** Vantaa; **Seppo K. Kaakkola,** Helsinki; **Pekka J. Kairisalo,** Helsinki; **Inge-Britt Y. Linden,** Helsinki; **Pekka I. Männistö,** Helsinki; **Erkki A. O. Nissinen,** Espoo; **Pentti Pohto,** Helsinki; **Aino K. Pippuri; Jarmo J. Pystynen,** both of Espoo, all of Finland

[73] Assignee: **Orion-yhtymä Oy,** Espoo, Finland

[21] Appl. No.: **121,617**

[22] Filed: **Sep. 16, 1993**

Related U.S. Application Data

[60] Division of Ser. No. 987,245, Dec. 7, 1992, Pat. No. 5,283,352, which is a continuation of Ser. No. 792,655, Nov. 15, 1991, abandoned, which is a division of Ser. No. 587,791, Sep. 25, 1990, Pat. No. 5,112,861, which is a division of Ser. No. 126,911, Nov. 27, 1987, Pat. No. 4,963,590.

[30] **Foreign Application Priority Data**

Nov. 28, 1986 [FI] Finland 864875
May 27, 1987 [GB] United Kingdom 8712437

[51] **Int. Cl.**[6] **C07C 205/22;** C07C 255/50

[52] **U.S. Cl.** **558/401;** 558/404; 558/414; 564/166; 564/167; 564/169; 560/136

[58] **Field of Search** 558/401, 404, 414; 564/166, 167, 169; 560/136

[56] **References Cited**

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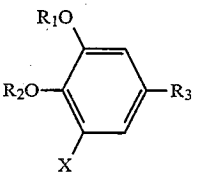
(List continued on next page.)

Primary Examiner—Jacqueline Haley
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis

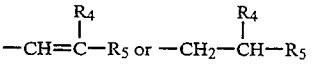
[57] **ABSTRACT**

A compound according to formula 1



1

wherein R_1 and R_2 independently represent hydrogen, carbamoyl which is substituted by an alkyl of 1 to 4 carbon atoms, alkylcarbonyl of 2 to 5 carbon atoms or phenyl carbonyl, X represents halogen nitro or cyano and R_3 represents



wherein R_4 represents cyano or alkylcarbonyl of 2 to 5 carbon atoms and R_5 represents carbamoyl which is unsubstituted or substituted with alkyl of 1 to 8 carbon atoms or which is substituted with hydroxyalkyl of 1 to 8 carbon atoms or pharmaceutically acceptable esters and salts thereof, and a pharmaceutically acceptable carrier therefor, as well as pharmaceutical compositions containing said compounds as COMT inhibitors.

4 Claims, 2 Drawing Sheets

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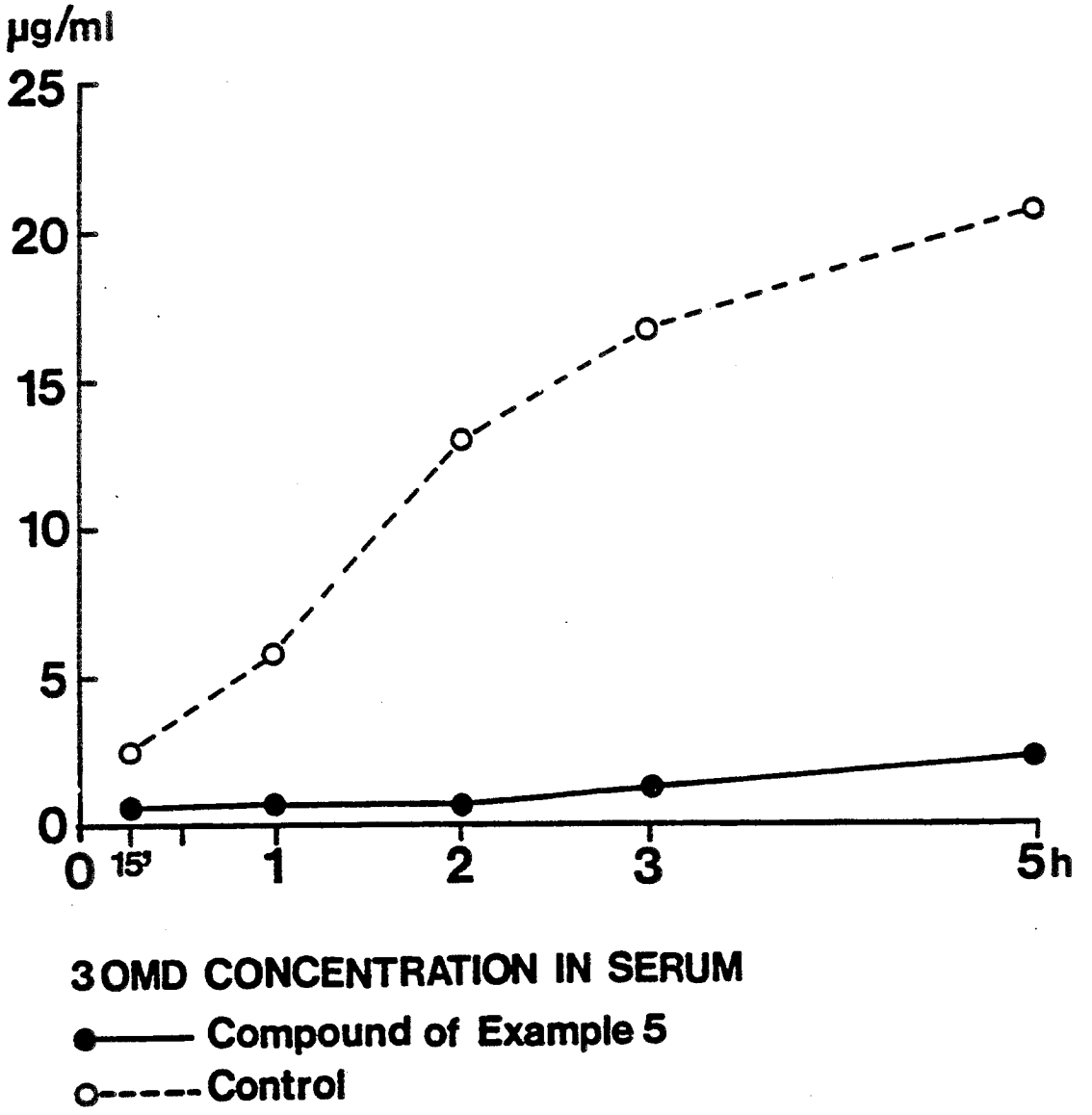
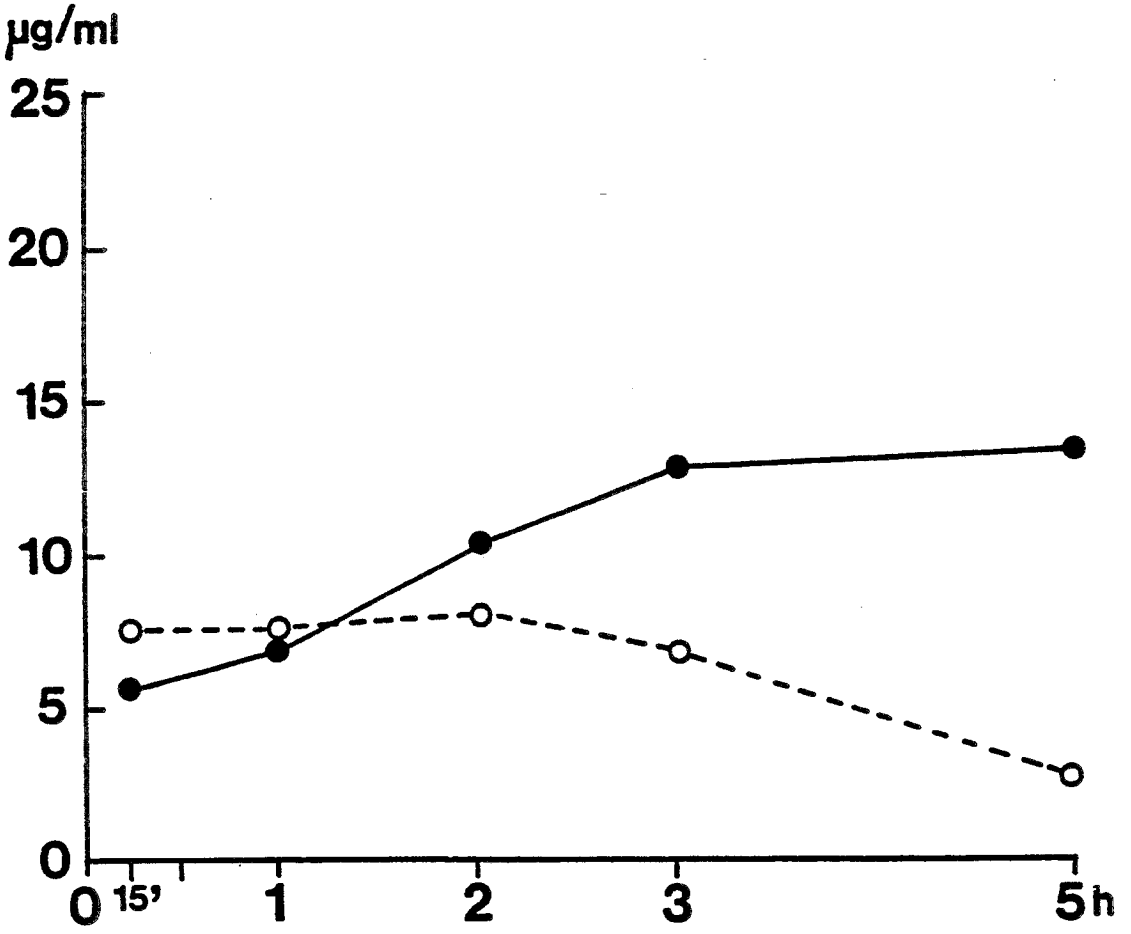

µg/ml
25
20
15
10
5
0
0
15'
1
2
3
5h
3 OMD CONCENTRATION IN SERUM
Compound of Example 5
Control

Fig. 1



L-DOPA CONCENTRATION IN SERUM

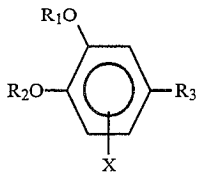
●—— Compound of Example 5

o----- Control

Fig. 2

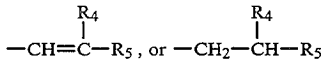
PHARMACOLOGICALLY ACTIVE CATECHOL DERIVATIVES

This application is a divisional of Application Ser. No. 07/987,245, filed Dec. 7, 1992, now U.S. Pat. No. 5,283,352, which is a continuation of Application Ser. No. 07/792,655, filed Nov. 15, 1991, now abandoned, which is a divisional of application Ser. No. 07/587,791, filed Sep. 25, 1990, now U.S. Pat. No. 5,112,861, which is a divisional of application Ser. No. 07/126,911, filed Nov. 27, 1987, now U.S. Pat. No. 4,963,590. The present invention relates to new pharmacologically active catechol derivatives according to formula I

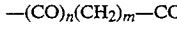


I

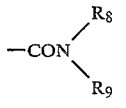
wherein R_1 and R_2 independently comprise hydrogen, alkyl, optionally substituted acyl or optionally substituted aroyl, lower alkylsulfonyl or alkylcarbamoyl or taken together form a lower alkylidene or cycloalkylidene group, X comprises electronegative substituent such as halogen, nitro, cyano, lower alkylsulfonyl, sulfonamido, trifluoromethyl, aldehyde or carboxyl and R_3 comprises hydrogen, halogen, substituted alkyl, hydroxyalkyl, nitro, cyano, optionally substituted amino, trifluoromethyl, lower alkylsulfonyl, sulfonamide, aldehyde, alkylcarbonyl, aralkylidenecarbonyl or carboxyl group or a group selected from



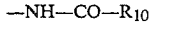
wherein R_4 comprises hydrogen, alkyl, amino, cyano, carboxyl or acyl and R_5 comprises hydrogen, amino, cyano, carboxyl, alkoxycarbonyl, carboxyalkenyl, nitro, acyl, hydroxyalkyl, carboxyalkyl, COZ, wherein Z is an optionally substitutted heterocyclic ring or one of following optionally substituted groups; carboxamido, carbamoyl, aroyl or heteroaryl or R_4 and R_5 together form a five to seven membered substituted cycloalkanone ring;



wherein n is 0–1, m is 0–7 and R comprises alkyl, hydroxy, carboxyalkyl, optionally substituted alkene, optionally substituted heterocyclic ring, alkoxy or substituted amino;



wherein R_8 and R_9 independently comprise hydrogen or one of the following optionally substituted groups; alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl or taken together form an optionally substituted piperidyl group;



wherein R_{10} comprises a substituted alkyl group.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the 3-LMD serum concentrations for the new compound and for a control compound which does not contain a COMT inhibitor.

FIG. 2 shows the levodopa serum concentrations after the same treatments.

The term "alkyl" as employed herein by itself or as part of another group includes both straight and branched chain radicals of up to 18 carbon atoms, preferably 1 to 8 carbon atoms, most preferably 1 to 4 carbon atoms. The term "lower alkyl" as employed herein by itself or as part of another group includes both straight and branched chain radicals of 1 to 7, preferably 1 to 4, most preferably i or 2 carbon atoms. Specific examples for the alkyl and lower alkyl residues, respectively, are methyl, ethyl, propyl, isopropyl, butyl, tert. butyl, pentyl, hexyl, octyl, decyl and dodecyl including the various branched chain isomers thereof.

The term "alkenyl" and "alkynyl" designate a hydrocarbon residue as defined above with respect to the term "alkyl" including at least one carbon to carbon double bond and carbon to carbon triple bond, respectively. The alkenyl and alkynyl residues may contain up to 12, preferably 1 to 8, most preferably 1 to 4 carbon atoms.

The term "acyl" as employed herein by itself or as part of another group refers to an alkylcarbonyl or alkenylcarbonyl group, the alkyl and alkenyl groups being defined above.

The term "aroyl" as used herein by itself or as part of another group refers to an arylcarbonyl group, the aryl group being a monocyclic or bicyclic group containing from 6 to 10 carbon atoms in the ring portion. Specific examples for aryl groups are phenyl, naphtyl and the like.

The term "lower alkylidene" refers to a chain containing from 2 to 8, preferably 2 to 4 carbon atoms. In a similar way the term "cycloalkylidene" refers to a cyclic hydrocarbon group containing 3 to 8, preferably 5 to 7 carbon atoms.

The term "alkoxy" as employed herein by itself or as part of another group includes an alkyl residue as defined above linked to an oxygen atom.

The term "cycloalkyl" includes saturated cyclic hydrocarbon groups containing 3 to 8, preferably 5 to 7 carbon atoms. Specific examples are the cyclopentyl, cyclohexyl, cycloheptyl and adamantyl groups.

The term "aralkyl" as employed herein refers to alkyl groups as defined above having an aryl substituent. A specific example is the benzyl group.

The term "halogen" as used herein refers to chlorine, bromine, fluorine or iodine, chlorine and bromine being preferred.

The term "optionally substituted" as used herein in connection with various residues refers to halogen substituents, such as fluorine, chlorine, bromine, iodine or trifluoromethyl groups, alkoxy, aryl, alkyl-aryl, halogen-aryl, cycloalkyl, alkylcycloalkyl, hydroxy, alkylamino, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, or alkylthio substituents.

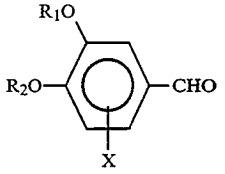
The "optionally substituted" groups may contain 1 to 3, preferably 1 or 2, most preferably I of the above mentioned substituents.

The term "heteroaroyl" or "heteroaryl" or "heteroalkyl" as employed herein refers to monocyclic-or bicy-

clic group containing 1 to 3, preferably 1 or 2 heteroatoms N and/or O and/or S. Specific examples are morfolinyl, piperidyl, piperidinyl, piperazinyl, pyridyl, pyrrolyl, quinolinyl and quinolyl.

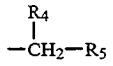
The invention also relates to pharmaceutically acceptable salts of the present compounds.

The present invention also relates to methods for the preparation of compounds of formula I. In accordance with the present invention compounds of formula I may be prepared for instance so, that an aldehyde of formula II



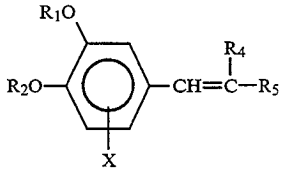
II

wherein R_1, R_2 and X are as defined above, is condensed in a base or acid catalyzed reaction with a compound of formula III



III

having an active methyl or methylene group and wherein R_4 and R_5 are as defined above, giving the compounds of formula Ia



Ia

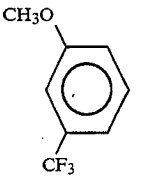
wherein R_4 and R_5 are as defined above and wherefrom the double bond optionally may be reduced to a single bond.

The compounds according to formula. II are also, in addition to being valuable medicines according to the present invention, new valuable intermediates for preparing other valuable products according to the invention.

Compounds of formula II wherein x is a cyano group can be prepared from the corresponding compounds, wherein X is halogen, preferably bromine, by allowing these compounds to react with cuprous cyanide in a polar, aprotic solvent, such as pyridine, N-methylpyrrolidone or N,N-dialkylformamide at elevated temperature (100°–200° C.).

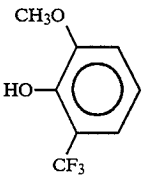
Alternatively the compounds of formula II, wherein X is a 5-cyano group can be prepared by formylation of 2,3-dihydroxybenzonitrile with hexamethylenetetramine.

Compounds of formula II, wherein X is 5-trifluoromethyl can be prepared starting from 3-methoxytrifluoromethylbenzene of formula XIV



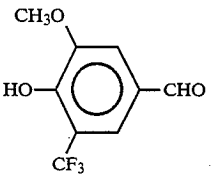
XIV

which compound is treated first with butyllithium and then with trimethylborate and further with performic acid to give the compound of formula XV



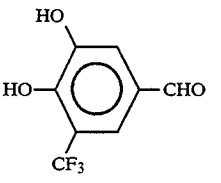
XV

which compound is formylated with hexamethylenetetramine in trifluoroacetic acid to give a compound of formula XVI



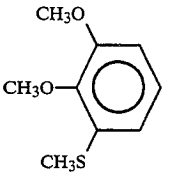
XVI

which compound is, if desired, demethylated for example with boron tribromide to give the compound of formula XVII



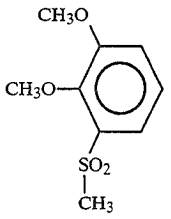
XVII

Compounds of formula II, wherein X comprises a 5-methylsulfonyl group, can be prepared from 2,3-dimethoxythioanisole of the formula XVIII



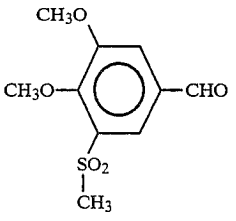
XVIII

which compound is treated first for example with peroxyacetic acid to give the corresponding sulfone of formula XIX



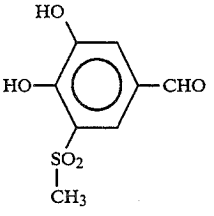
XIX

which compound is then formylated with hexamethylenetetramine in trifluoroacetic acid to give the compound of formula XX



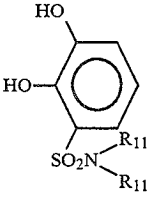
XX

which compound may be, if desired, demethylated (HSr or SBr_3) to give a compound of formula XXI



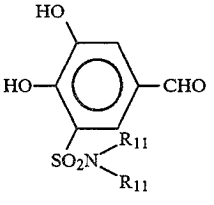
XXI

The compound of formula II, wherein X comprises sulfonamido, can be prepared by formylation of 2,3-dihydroxybenzenesulfonamide of formula XXII



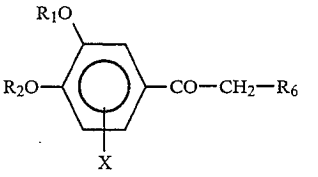
XXII

wherein R_{11} means hydrogen or alkyl, to give the compound of formula XXIII



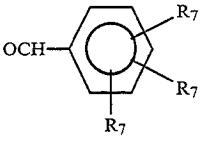
XXIII

Alternatively compounds of formula I according to the present invention can be prepared from a ketone of formula IV



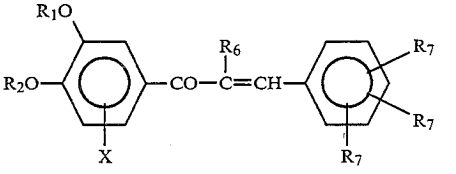
IV

wherein R_1, R_2, x are as defined above and R_6 comprises hydrogen or alkyl, by a condensation with an aldehyde of formula V



V

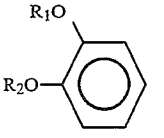
wherein R_7 comprises hydrogen, alkyl, alkoxy or dialkylamino to give the compounds of formula Ib



Ib

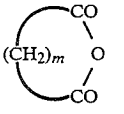
wherein R_1, R_2, X, R_6 and R_7 are as defined above.

Alternatively compounds of formula I, wherein R_3 comprises a substituted alkyl group can be prepared by Friedel-Craft's reaction from a compound of formula VI



VI

wherein R_1 and R_2 are as defined above by allowing the compound of the formula VI to react in the presence of aluminium chloride either with a cyclic acid anhydride of formula VII

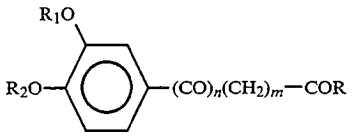


VII

wherein m is 1–7 or alternatively with a dicarboxylic acid ester chloride of formula VIII

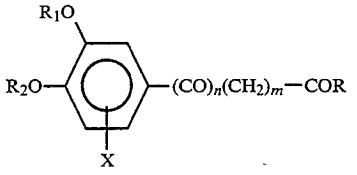
VIII

wherein m is 0–7 and n is 0–1 and R is as defined above and Hal is a halogen atom, to give the compounds of formula IX



IX

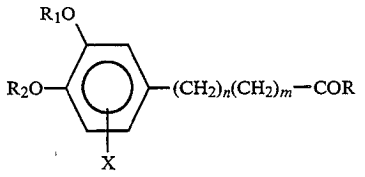
wherein the aromatic ring will be substituted with the group X to give the compounds of formula Ic



Ic

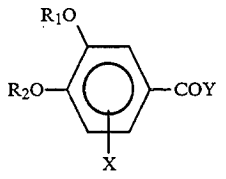
wherein R, R_1, R_2 and X are as defined above.

In the compounds of formula Ic the carbonyl group can be reduced to a methylene group by conventional methods (Clemmensen and Wolff-Kischner reduction) to give compounds of formula Id



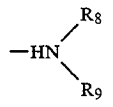
Id

The compounds according to the present invention, wherein R_3 comprises a substituted carbamido group, can be prepared by allowing an activated benzoic acid derivative of formula X



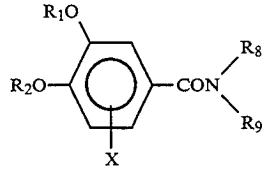
X

wherein R_1, R_2 and X are as defined above and Y comprises halogen or some other activated group to react with an amine of formula XI



XI

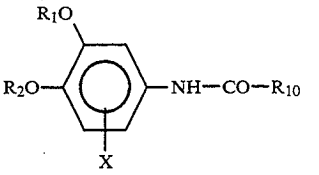
wherein R_8 and R_9 are as defined above to give compounds of formula Ie



Ie

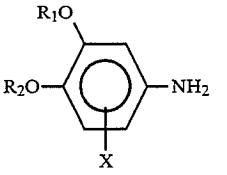
wherein R_1, R_2, X, R_8 and R_9 are as defined above.

The compounds of formula I, wherein R_3 is an acylated amino group having formula If



If

wherein R_1, R_2, X and R_{10} are as defined above can be prepared by allowing an aniline derivative of formula XII



XII

wherein R_1, R_2 and X are as defined above, to react with an activated carboxylic acid derivative of formula XIII

$$Y—CO—R_{10} \qquad \text{XIII}$$

wherein Y and R_{10} are as defined above.

The invention relates to compositions where the compounds of formula I may be used as the active medicine. The compositions may contain the compounds of formula I alone or combined with some other medicines. For the treatment of Parkinson's disease the compounds according to formula I are given with levodopa, each in its own composition or combined in one composition. Also peripheral dopa decarboxylase (DDC) inhibitors, such as carbidopa or benserazide may be present, even though they are not obligatory.

The compounds according to this invention may be given in different dosage forms for administering in any suitable enteral or parenteral way. The dosage forms, like tablets, pills, injection liquids etc may be manufactured by the known principles in the art. One can use any pharmaceutically accepted additives, lubricants, fillers etc to modify different properties of the dosage forms.

Catechol-0-methyltransferase (COMT) catalyzes the transfer of the methyl group from S-adenosyl-n-methionine to a number of compounds with catechol structures. This enzyme is important in the extraneuronal inactivation of catecholamines and drugs with catechol structures. COMT is one of the most important enzymes involved in the metabolism of catecholamines. It is present in most tissues, both in the periphery and the central nervous system. The highest activities are found in the liver, intestine and kidney. COMT probably is present in soluble and membrane bound forms. The exact character of the two forms has not been established.

In Parkinson's disease the dopaminergic neurones, primarily the nigrostriatal neurones, are damaged, gausing dopamine deficiency in the cerebral basal ganglia. This deficiency can be compensated by levodopa which is converted to dopamine in the central nervous system under the influence of DDC.

Today, levodopa treatment is almost invariably supplemented with a peripheral DDC inhibitor to inhibit too early dopamine formation and thereby to increase

the cerebral levodopa concentration and to decrease the peripheral side effects of dopamine.

In addition to DDC, COMT metabolizes levodopa, converting it to 3-0-methyldopa (3-OMD). 3-OMD readily penetrates the blood-brain barrier via an active transport system. Alone it is therapeutically ineffective and detrimental when competing with levodopa. 3-OMD is accumulated in tissues because of its long half-life (ca. 15 h) compared to levodopa (ca. 1 h). The high activity of COMT clearly correlates with the poor efficacy of levodopa despite the presence of peripheral DDC inhibitor.

In addition to monoamine oxidase (MAO), COMT is a major enzyme participating in the amine metabolism. By inhibiting the metabolism of endogenous amines (dopamine, noradrenaline, adrenaline) in the brain the COMT inhibitors decrease decomposition of these compounds. Thus they may be useful in the treatment of depression.

By inhibiting peripheral COMT effectively, COMT inhibitors direct the metabolic route of levodopa towards decarboxylation, forming thereby more dopamine which is important in the treatment of hypertension and heart failure.

It has been unexpectedly observed that the compounds according to the invention are extremely effective COMT inhibitors. They open up new, previously unknown possibilities in the treatment of Parkinson's disease. In addition the new compounds may be useful also in the treatment of depression and heart failure as well as hypertension.

The new COMT inhibitors, which inhibit formation of 3-OMD, may decrease the adverse effects of long-term use of levodopa. Furthermore, levodopa doses can be reduced. It has been shown that the dose of levodopa can be reduced by half or to one-third of the dose used without COMT inhibitor. Since dosage of levodopa is individual, it is difficult to give any absolute dosage, but daily doses as low as 25–50 mg have been considered sufficient to start with.

A preliminary clinical trial on n-butyl gallate, a known COMT inhibitor, showed patients with Parkinson's disease clearly to benefit of n-butyl gallate. The study was, however, discontinued because of the too high toxicity of n-butyl gallate.

The COMT inhibitory efficacy of the compounds according to the invention was tested using the following experimental procedures.

Determination of COMT activity in vitro

The in vitro activity of COMT was determined in enzyme preparations isolated from the brain and liver of female Han:WIST rats, weight ca. 100 g. The rats were killed by carbon dioxide, and the tissues were removed and stored at −80° C. until determination of enzyme activity.

The enzyme preparation was prepared by homogenizing the tissues in 10 mM phosphate buffer, pH 7.4, (1:10 weight g/ml) which contained 0.5 mM dithiotreitol. The homogenate was centrifuged 15000 x G for 20 min. The supernatant was recentrifuged 100000 x G for 60 min. All procedures were done at +4° C. The supernatant of the last centrifugation (100000 x G) was used to determine the activity of soluble COMT enzyme.

Determination of IC_{50} was performed by measuring the COMT activity in several drug concentrations of the reaction mixture which contained the enzyme preparation, 0.4 mM dihydroxybenzoic acid (substrate), 5 mM magnesium chloride, 0.2 mM S-adenosyl-L-methionine and COMT inhibitor in 0.1 M phosphate buffer, pH 7.4.No COMT inhibitor was added to the control. The mixture was incubated for 30 min at 37° C. whereafter the reaction was stopped by perchloric acid and the precipitated proteins were removed by centrifugation (4000 x G for 10 min). The activity of the enzyme was measured by determining the concentration of 3-methoxy-4-hydroxybenzoic acid formed from the substrate of COMT (dihydroxybenzoic acid) by HPLC using an electrochemical detector. Chromatography was performed by injecting 20 µl of the sample in a 4.6 mm×150 mm Spherisorb ODS column (particle size 5 µm). The reaction products were eluted from the column with 20% methanol containing 0.1 M phosphate, 20 mM citric acid and 0.15 mM EDTA, pH 3.2, at a flow rate of 1.5 ml/min. The electrochemical detector was set to 0.9 V against an Ag/AgCl electrode. The concentration of the reaction product, 3-methoxy-4-hydroxybenzoic acid, was compared with the control samples and the samples containing COMT inhibitor. The IC50 value is the concentration which causes a 50% decrease in COMT activity.

Effect of COMT inhibitors in vivo

Male Han:WIST rats, weight 200–250 g, were used in the experiment. The control group was given 50 mg/kg carbidopa 30 min before levodopa (50 mg/kg). The test group was also given carbidopa 50 mg/kg 30 min before levodopa+COMT inhibitor. The drugs were administered orally.

Sampling

About 0.5 ml of blood was drawn from the tail artery. The sample was allowed to coagulate in ice. Thereafter the sample was centrifuged and serum separated. Serum was stored at −80° C. until determination of concentrations of levodopa and its metabolite 3-OMD.

Determination of levodopa and 3-OMD serum concentrations

To serum (e.g. 100 µl), an equal volume of 0.4 M perchloric acid, 0.1% sodium sulphate, 0.01% EDTA, which contained dihydroxybenzylamine as internal standard, were added. The sample was mixed and kept in ice, whereafter the proteins were removed by centrifugation (4000 x G for 10 min.) and the concentrations of levodopa and 3-OMD were determined by HPLC using an electrochemical detector. The compounds were separated in a 4.6 mm×150 mm Ultrasphere ODS column in an eluent containing 4% acetonitrile, 0.1 M phosphate buffer, 20 mM citric acid, 0.15 mM EDTA, 2 mM octylsulphonic acid and 0.2% tetrahydropholan, pH 2.8. The flow rate was 2 ml/min. The electrochemical detector was set to +0.8 V against an Ag/AgCl electrode. The concentrations of the test compounds were determined by comparing the heights of the peaks with that of the internal standard. The ratio was used to calculate the serum concentrations of levodopa and 3-OMD in control rats and those given COMT inhibitor.

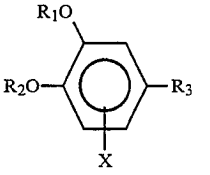
Results

The best COMT inhibitors according to the invention were more than thousand times more potent in vitro than the most potent known reference compound U-0521 (Table I). Also the orally administered COMT

inhibitors were shown to inhibit the formation of serum 3-OMD significantly more than U-0521 (Table II). The reference compound U-0521 furthermore penetrated the blood-brain barrier and inhibited the thyrosine hydroxylase activity thereby blocking the biosynthesis of vitally important catecholamines. In contrast the compounds according to the invention are COMT specific and they do not significantly penetrate the blood-brain barrier.

Results in vitro

TABLE 1



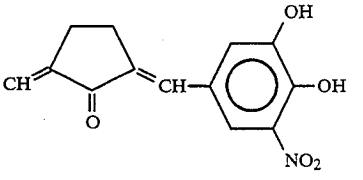
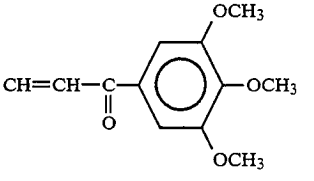
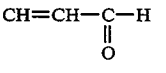
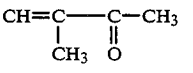
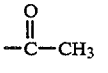
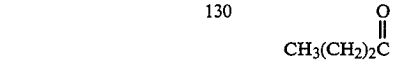
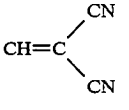
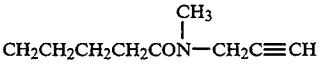
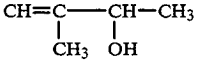
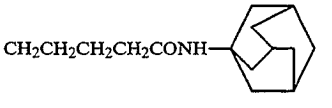
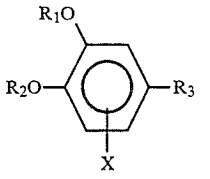
Example compound	R_1	R_2	X	R_3	COMT-INHIBITION IN BRAIN TISSUE (IC50(nM)
79	H	H	5-NO_2		3
11	H	H	5-NO_2		5
8	H	H	5-NO_2		6
6	H	H	5-NO_2		12
110	H	H	5-NO_2	NO_2	12
109	H	H	5-NO_2		16
130		H	5-NO_2	NO_2	18
5	H	H	5-NO_2		20
27	H	H	5-NO_2		20
16	H	H	5-NO_2		23
111	H	H	5-NO_2		24
113	H	H	5-NO_2	—Cl	25
112	H	H	5-NO_2	—CN	30
28	H	H	5-NO_2		27

TABLE 1-continued



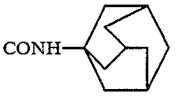
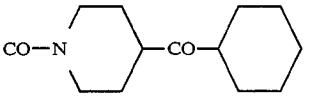
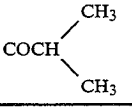
Example compound	R_1	R_2	X	R_3	COMT-INHIBITION IN BRAIN TISSUE (IC50(nM)
26	H	H	5-NO_2	$CH_2CH_2CH_2CH_2CONH-CH(CH_3)_2$	33
3	H	H	5-NO_2	CH=CH—COOH	37
128	$CH_3CH_2C(=O)O$	$CH_3CH_2C(=O)O$	5-NO_2	NO_2	60
127	$CH_3C(=O)O$	$CH_3C(=O)O$	5-NO_2	75	
24	H	H	5-NO_2	$CH_2CH_2CH_2CH_2COOH$	90
109	H	H	5-NO_2	—H	140
131	$(CH_3)_3CC(=O)O$	H	5-NO_2	NO_2	220
41	H	H	6-NO_2	$CH_2CH_2CH_2CH_2COOH$	380
54	H	H	5-Cl		400
67	CH_3CO	CH_3CO	6-NO_2		750
U-0521	H	H	5-H		6000

TABLE 2

		In vivo results	
		3-OMD concentration % of control	
Oral dose	Compound	1 h	5 h
3 mg/kg	Example 110	−97	−80
4.3 mg/kg	Example 127	−67	−76
4.7 mg/kg	Example 128	−70	−77
4.3 mg/kg	Example 131	−92	−83
4.1 mg/kg	Example 130	−98	−92
30 mg/kg	Example 19	−99	−76
30 mg/kg	Example 111	−100	−65
30 mg/kg	Example 5	−96	−89
30 mg/kg	Example 6	−84	−49
30 mg/kg	Example 11	−63	−26
30 mg/kg	Example 8	−58	−34
100 mg/kg	Example 24	−86	−41
100 mg/kg	U−0521	−34	−14

The results indicate that the compounds according to the invention are even more than thousand times more potent in vitro (Table 1) than the reference coumpound (U-0521). The orally administered new compounds inhibit COMT also in vivo significantly better than the reference compound, which is reflected as decreased serum 3-OMD concentration (Table 2). The reference compound U-0521 furthermore penetrates the blood-brain barrier and nonspecifically inhibits thyrosine hydroxylase which is essential for the biosynthesis of catecholamines.

FIG. **1** shows the 3-OMD serum concentrations for the new compound (e.g. according to example 5) and for the control compound which does not contain COMT inhibitor. The experimental design is the same as for the in vivo experiments above. FIG. **2** shows the levodopa serum concentrations after the same treatments. These figures show that the compounds according to the invention increase the bioavailability of levodopa and decrease the level of the harmful metabolite 3-OMD. The change observed in serum is reflected in the brain concentrations of 3-OMD and levodopa.

Specificity of COMT inhibition

The new compounds are specifically comt inhibitors and not inhibitors of other essential enzymes. This was

shown in in vitro experiments which were performed as described above.

	IC_{50} (nM)					
Compound	COMT	TH	DBH	DDC	MAO-A	MAO-B
Example 87	3	38.000	>50.000	>50.000	>50.000	>50.000
Example 11	5	18.000	>50.000	>50.000	>50.000	>50.000
Example 8	6	21.000	>50.000	>50.000	>50.000	>50.000
Example 6	12	50.000	>50.000	>50.000	>50.000	>50.000
Example 110	12	14.000	>50.000	>50.000	>50.000	>50.000
Example 19	16	17.500	>50.000	>50.000	>50.000	>50.000
Example 5	20	21.000	>50.000	>50.000	>50.000	>50.000
Example 111	24	50.000	>50.000	>50.000	>50.000	>50.000
U-0521	6000	24.000	>50.000	>50.000	>50.000	>50.000

TH=Thyrosine hydroxylase, DBH=Dopamine-β-hydroxylase MAO-A and -B=Monoamine oxidase-A and -B.

The COMT inhibitors according to the invention are extremely specific. They inhibit COMT effectively at low concentrations, while inhibition of other enzymes involved in the metabolism of catecholamines requires a 1000–10000 times higher concentration. The difference between the inhibition of TH and COMT in the reference compound U-0521 is only 4-fold.

IC_{50} is the concentration which inhibits 50% of the enzyme activity.

Toxicity

The new COMT inhibitors are non-toxic. For instance, the LD_{50} of 3-(3,4-dihydroxy-5-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (Example 11) given as an oral suspension to rats, was over 2500 mg/kg.

EXAMPLE 1

3-Nitro-5-[2-(4-pyridyl)vinyl]catechol

A solution containing 2.0 g (0.011 mole) of 3,4-dihydroxy-5-nitrobenzaldehyde and 2.23 g (0,024 mole) of 4-picoline in 9.0 ml of acetic anhydride was refluxed for 1 h. About 15 ml of isopropanol was then added and the solution was cooled to 0° C. where upon the diacetyl-derivative of the desired product crystallized. After filtration the product was suspended in 100 ml of 0.5 N hydrochloric acid and refluxed for 1.5 h. After cooling the precipitate was filtered, washed with water and acetone and dried. Yield 1.89 g (67%), m.p. above 350° C.

EXAMPLE 2

3-Nitro-5-[2-(4-quinolyl)vinyl]catechol

The same procedure described in Example 1 was repeated using 2.0 g (0.011 mole) of 3,4-dihydroxy-5-nitrobenzaldehyde and 3.44 g (0.024 mole) of.4-quinaldine. Yield 1.7 g (50%), m.p. 250° C. (decomp.).

EXAMPLE 3

4-Hydroxy-3-methoxy-5-nitrocinnamic acid

A solution of 1.0 g of 5-nitrovanillin and 4.0 g of malonic acid in 10 ml of pyridine was heated for 50 h at 80° C. The reaction mixture was diluted with water, acidified with hydrochloric acid, filtered, washed with water and dried. Yield 0.44 g (36%). The ^{1}H-NMR spectrum was in accordance with the structure alleged.

EXAMPLE 4

3,4-Dihydroxy-5,ω-dinitrostyrene

A solution containing 3.66 g (0.02 mole) of 3,4-dihydroxy- 5-nitrobenzaldehyde, 3.66 g (0.06 mole) of nitromethane and 3.31 g of ammonium acetate in 10 ml of abs. ethanol was refluxed for 6 h. Water was added to the reaction mixture. The mixture was acidified with hydrochloric acid and extracted with methylene chloride. The methylene chloride extract was washed with water and the solvent was evaporated in vacuo. The residue was crystallized from isopropanol, yield 1.9 g (40%), m.p. 258°–260° C.

EXAMPLE 5

3,4-Dihydroxy-5-nitro-ω,ω-dicyanostyrene

The same procedure described in Example 4 was repeated using 3.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 3.0 g of malonodinitrile. The product was crystallized from methanol-water, yield 1.9 g (50%), m.p. 205°–209° C.

EXAMPLE 6

4-(3,4-Dihydroxy-5-nitrophenyl)-3-methylbut-3-en-2-one

A solution containing 0.5 g of 3,4-dihydroxy-5-nitrobenzaldehyde in 2.0 ml of butanone was saturated with gaseous hydrogen chloride. After standing over night ether was added to the solution and it was filtered. The product was crystallized from isopropanol, yield 0.2 g (30%), m.p. 139°–141° C.

EXAMPLE 7

3-(3,4-Dihydroxy-5-nitrobenzylidene)-2,4-pentanedione

A solution containing 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.00 g of 2,4-pentanedione in 10 ml of tetrahydrofuran was saturated with gaseous hydrogen chloride. After standing over night at 5° C. the product was filtered and washed with ether. Yield 1.2 g (50%), m.p. 175°–178° C.

EXAMPLE 8

3-(3,4-Dihydroxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

A solution containing 0.55 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 0.36 g of acetophenone in 10 ml of methanol was saturated with gaseous hydrogen chloride. After standing over night at 5° C. the product was filtered and washed with methanol. Yield 0.55 g (68%), m.p. 192°–195° C.

EXAMPLE 9

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(4-methoxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.8 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.5 g of 4'-methoxyacetophenone in 20 ml of tetrahydrofuran. Yield 1.88 g (60 m.p. 222°–228° C.

EXAMPLE 10

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(3,4-dimethoxyphenyl)prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.8 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 18 g of 3',4'-dimethoxyacetophenone in 20 ml of methanol. Yield 1.7 g (50%), m.p. 206°–208° C.

EXAMPLE 11

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 0.55 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 0.63 g of 3',4',5'-trimethoxyacetophenone Yield 0.50 g (44%), m p 213°–216° C.

EXAMPLE 12

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(2-hydroxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 0.74 g of 2'-hydroxyacetophenone. Yield 0.2 g (12%), m.p. 231°–234° C.

EXAMPLE 13

3-(3,4-Diacetoxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

A solution containing 1.0 g of the product obtained in Example 8 in 5.0 ml of acetic anhydride was refluxed for 2 h. After cooling the product was filtered and washed with ether. Yield 0.73 g (68%), m.p. 183°–185° C.

EXAMPLE 14

3-(3,4-Dibenzoyloxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

1.0 g of the product obtained in Example 8 and 2.0 ml of benzoylchloride were dissolved in 5 ml of tetrahydrofuran. Tetrahydrofuran was distilled off to a great extent and the residue was refluxed for 2 h. After cooling ether was added to the mixture and the product was filtered and triturated with ethylmethylketone. Yield 0.50 g (29%), m.p. 206°–210° C.

EXAMPLE 15

3-(3-Pivaloyloxy-4-hydroxy-5-nitrophenyl)-1-phenyl-prop-2-en-1-one

1.0 g of the product obtained in Example 8 was dissolved in 5 ml of tetrahydrofuran, 4.7 ml of pivaloyl chloride was added and the mixture was refluxed for 16 h. The solvent was evaporated in vacuo and the residue was purified in a silicagel column by using toluene-acetic acid-dioxane (18:1:1) mixture as an eluent. The product was crystallized from ether, m.p. 148°–150° C.

EXAMPLE 16

4-(3,4-Dihydroxy-5-nitrophenyl)-3-methylbut-3-en-2-ol

1.8 g of the product obtained in Example 6 was dissolved in 20 ml of 1N NaOH-solution and 4.0 g of sodium borohydride in small amount of water was added. The mixture was stirred over night at room temperature, acidified with hydrochloric acid and extracted with ether. The solvent was evaporated in vacuo and the residue purified in a silica gel column by using toluene-acetic acid dioxane (18:1:1). The product was crystallized from dichloromethane petroleum ether. Yield 0.80 g (44%), m.p. 102°–104° C.

EXAMPLE 17

7-(3,4-Dihydroxy-5-nitrobenzylidene)-8-ketononanoic acid

The procedure described in Example 9 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.72 g of 8-ketononanoic acid. Yield 1.85 g (55%), yellow viscous oil.

EXAMPLE 18

4'-Hydroxy-3'-methoxy-5'-nitroacetophenone

To a solution containing 40 ml of nitric acid (d-1.41) and 40 ml of water was gradually added while cooling (below 7° C.) and stirring 25.0 g of 4'-hydroxy-3'-methoxyacetophenone. After stirring for 0.5 h at 0° C. the product was filtered, washed first with diluted nitric acid (1:1) and then with water. Yield 24.0 g (75%). The ^{1}H-NMR-spectrum of the product was in accordance with the structure alleged.

EXAMPLE 19

3,4,-Dihydroxy-5'-nitroacetophenone

A solution containing 19.9 g of the product obtained in Example 18 in 200 ml of acetic acid and 200 ml of 48% hydrobromic acid was refluxed for 5 h. 500 ml of a saturated solution of sodium sulfate was added to the reaction mixture and the same was let stand overnight at 5° C. The solution was extracted with ether. The ether phase was washed with 200 ml of water, dried and the solvent evaporated in vacuo. The residue was crystallized from isopropanol. Yield 10.2 g (55 m.p. 155°–159° C.

EXAMPLE 20

1-(3,4-Dihydroxy-5-nitrophenyl)-3-(4-dimethylaminophenyl)-prop-2-en-1-one

A solution containing 0.5 g of the product obtained in Example i9 and 0.38 g of 4-dimethylaminobenzaldehyde in 5 ml of methanol was saturated with gaseous hydrogen chloride. The solution was refluxed for 1 h. After cooling the product was filtered and washed with methanol. Yield 0.26 g (70%), decomp. on heating.

EXAMPLE 21

5-(4-Benzyloxy-3-methoxyphenyl)-2,4-pentadienoic acid

To a solution containing 260 g of 4-benzyloxy-3-methoxybenzaldehyde and 200 ml of ethyl crotonate in 1200 ml of N-methylpyrrolidone was gradually added while stirring and cooling at 0° C. 149.6 g of potassium tert.-butoxide. The solution was stirred for 0.5 h after which 200ml of 10 N NaOH-solution was added and

stirred for 0.5 h more at 0° C. The reaction mixture was added to a mixture of hydrochloric acid and ice. The semisolid product was separated and used without purification to the next step.

EXAMPLE 22

(4-Hydroxy-3-methoxyphenyl)pentanoic acid

The raw product obtained in Example 21 was dissolved in 500 ml of N,N-dimethylformamide and 22 g of 10% palladium on charcoal catalyst was added. The mixture was hydrogenated at 60° C. and normal pressure until the theoretical amount (3 mole) of hydrogen was consumed. After filtering the solvent was evaporated in vacuo to a great extent and the residue was dissolved in 11 of dichloromethane and washed with 2 1 of water. The product was extracted with 1.5 1 of saturated $NaHCO_3$-solution. After acidification of the aqueous phase with hydrochloric acid the product was extracted with 1 l of dichloromethane. The solvent was distilled off in vacuo and the semisolid residue (180 g) was used to the next step.

EXAMPLE 23

5-(4-Hydroxy-3-methoxy-5-nitrophenyl)pentanoic acid

The above product (180 g) was dissolved in 1 l of dichloromethane and 820 ml of 1 molar HNO_3-dichloromethane solution was added gradually while stirring and cooling (0°–5° C.). The solution was stirred for 10 min more at 0° C. after which water was added. The organic phase was separated and washed with water. The solvent was evaporated in vacuo and the semisolid residue was used as such to the next step.

EXAMPLE 24

5-(3,4-Dihydroxy-5-nitrophenyl)pentanoic acid

The above product obtained in Example 23 was dissolved in a mixture containing 500 ml of acetic acid and 500 ml of 48% hydrobromic acid and refluxed for 4 h. 1 l of saturated Na_2SO_4-solution was added to the reaction mixture and the solution was allowed to stand over night at 5° C. The product crystallized was filtered and washed with 50% acetic acid. This product was recrystallized from ethyl acetate. Yield 32 g (16%), m.p. 135°–138° C.

EXAMPLE 25

1-Benzyl-4-[5-(3,4-dihydroxy-5-nitrophenyl)pentanoyl-piperazine hydrochloride

A solution containing 3.0 g of the product obtained in Example 24 in 18 ml of thionyl chloride was refluxed for 10 min. The excess of thionyl chloride was evaporated in vacuo and the acid chloride formed was dissolved in 20 ml of dichloromethane. To this solution 2.1 g of 1-benzylpiperazine in 20 ml of dichloromethane was added with stirring and stirred for 0.5 h more. Ether was added to the reaction mixture and the crystals were filtered. Yield 3.55 g (73%), m.p. 85°–89° C.

EXAMPLE 26

N-Isopropyl-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic amide

A solution containing 0.5 g of the product obtained in Example 24 in 2.5 ml of thionyl chloride was refluxed for 10 min. The excess of thionyl chloride was evaporated in vacuo and the residue dissolved in 25 ml of dichloromethane. To this solution 0.47 g of isopropylamine was added and the mixture was Stirred for 1 h at 20° C. Dichloromethane phase was washed with 1 N hydrochloric acid and evaporated in vacuo. The residue was crystallized from toluene. Yield 0.44 g (75%), m.p. 113°–115° C.

EXAMPLE 27

N-Methyl (-N-propargyl-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic amide

The procedure described in Example 26 was repeated using 0.5 g of methyl propargylamine instead of isopropylamine. Yield 0.5 g (83%), mp. 133°–135° C.

EXAMPLE 28

N-(1-Adamantyl)-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic amide

The procedure described in Example 26 was repeated using 1.5 g of 1-aminoadamantane instead of isopropylamine. Yield 0.61 g (80%), m.p. 157°–160° C.

EXAMPLE 29

Tetradecyl-5-(3,4-dihydroxy-5-nitrophenyl)pentanoate

The procedure described in Example 26 was repeated using 1.26 g of 1-tetradecanol instead of isopropylamine. The reaction mixture .was washed with water and the solvent evaporated in vacuo. Yield 0.44 g (50%), m.p. 46°–47° C.

EXAMPLE 30

Tetradecyl-5-(3,4-diacetoxy-5-nitrophenyl)pentanoate

A solution containing 0.1 g of the product obtained in Example 29 in 2 ml of acetic anhydride was refluxed for 20 min. The solvent was evaporated in vacuo and the residue crystallized from petroleum ether (b.p. 40° C.), m.p. 52°–54° C.

EXAMPLE 31

Tetradecyl-5-(4-hydroxy-3-pivaloyloxy-5-nitrophenyl) pentanoate

The procedure described in Example 30 was repeated using 2 ml of pivaloyl chloride instead of acetic anhydride. The product was a viscous oil.

EXAMPLE 32

5-(3,4-Dimethoxy-5-chlorophenyl)-2,4-pentadienoic acid

To a solution containing 10.0 g of 3,4-dimethoxy-5-chlorobenzaldehyde and 8.3 ml of ethyl crotonate in 65 ml of N-methylpyrrolidone 6.7 g of potassium tert.-butoxide was added with stirring. The solution was stirred for 0.5 h more at 20° C. and the solution was poured then to a mixture of ice and hydrochloric acid and extracted with ether. The ether extract was washed with water and extracted then with $NaHCO_3$-solution. The aqueous phase was acidified with hydrochloric acid and the semisolid product was separated and washed with water. Yield 7.3 g (55%).

EXAMPLE 33

5-(3,4-Dimethoxy-5-chlorophenyl)pentanoic acid

A solution containing 6.2 g of the above product obtained in Example 32 was dissolved in a mixture of 30 ml of acetic acid and 3 ml of conc. hydrochloric acid. Palladium on charcoal catalyst (10% Pd) was added

and the mixture was hydrogenated at normal pressure and room temperature. After filteration the solvents were evaporated in vacuo. Yield 3.2 g (55%), a viscous oil.

EXAMPLE 34

5-(3,4-Dihydroxy-5-chlorophenyl)pentanoic acid

A solution containing 3.2 g of the above product in 8 ml of acetic acid and 10 ml of 48% hydrobromic acid was refluxed for 3 h. A saturated solution of Na_2SO_4 in water was added to the reaction mixture. The crystallized product was filtered, washed with water and recrystallized from toluene, m.p. 99°–101° C.

EXAMPLE 35

5-(3,4-Dimethoxy-6-chlorophenyl)-2,4-pentadienoic acid

To a solution containing 10.0 g 3,4 dimethoxy-6-chlorobenzaldehyde and 8 ml of ethyl crotonate in 60 ml of N-methylpyrrolidone 6.0 g of potassium tert.-butoxide was added while stirring. The solution was stirred for 0.5 h more at 20° C. and poured then to a mixture of ice and hydrochloric acid. The solution was extracted with ether. The ether solution was washed with water and extracted with 2.5 N NaOH-solution. The aqueous phase was acidified with hydrochloric acid and the semisolid product was separated. Yield 10.8 g (81%).

EXAMPLE 36

5-(3,4-Dihydroxy-6-chlorophenyl)-2,4-pentadienoic acid

To a solution containing 0.54 g of the product obtained in Example 35 in 6 ml dichloromethane 6 ml of 1 molar boron tribromide-dichloromethane solution was added and stirred for 24 h at 20° C. The solvent was evaporated in vacuo and 2 N hydrochloric acid was added to the residue. The product was filtered and washed with water. Recrystallization from isopropanol-water yielded 0.22 g (46%) of the product desired, m.p. 203–-206° C.

EXAMPLE 37

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(4-methylphenyl)-prop-2-en-1-one

A solution containing 5.49 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 5.37 g of 4'-methylacetophenone in 50 ml of tetrahydrofuran was added a catalytic amount of gaseous hydrogen chloride and refluxed for 4.5 h. The solvent was evaporated in vacuo and the residue crystallized from ether-petroleum-ether, yield 1.85 g (21%), m.p. 184°–186° C.

EXAMPLE 38

5-(3,4-Dimethoxyphenyl)-5-ketopentanoic acid

A solution containing 36 g of veratrole and 30 g glutaric anhydride in 120 ml of nitrobenzene was gradually added while stirring and cooling at 0° C. to a mixture of 72 g of anhydrous aluminium chloride and 240 ml of nitrobenzene. The mixture was stirred for 1 h at 0° C. and then for 18 h at 20° C. Ice and hydrochloric acid were added to the reaction mixture. Nitrobenzene layer was separated and to this ethyl acetate was added whereupon the product crystallized. After filtering the crystals were washed with ethyl acetate. Yield 42.3 g (64%).

EXAMPLE 39

5-(3,4-Dimethoxyphenyl)pentanoic acid

A mixture containing 37.6 g of the product obtained in Example 38 and 64 g of zinc turnings (treated with a solution of $HgCl_2$), 55 ml of toluene and 220 ml of cone. hydrochloric acid was refluxed for 1 h. Toluene phase was separated and evaporated in vacuo. The residue was crystallized from toluene-petroleum ether, yield 11.5 g (32%).

EXAMPLE 40

5-(3,4-Dimethoxy-6-nitrophenyl)pentanoic acid

15.0 g of product described in Example 39 was gradually added to 75 ml of nitric acid (d-1.41) at 20° C. The mixture was stirred for 20 min more. Ice-water was added and solution was extracted with dichloromethane. The solvent was evaporated in vacuo yielding 14.0 g (79%) of the desired product.

EXAMPLE 41

5-(3,4-Dihydroxy-6-nitrophenyl)pentanoic acid

A solution containing 42.0 g of the product obtained in Example 40 in 100 ml of acetic acid and 150 ml of 48% hydrobromic acid was reflexed for 10 h. 1 l of saturated Na_2SO_4-solution was added to the reaction mixture and extracted with ether. The solvent was evaporated in vacuo and the residue crystallized from ethyl acetate-petroleum ether. Yield 7.9 g (19%), m.p. 111°–114° C.

EXAMPLE 42

3-(3,4-Dimesyloxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

A solution containing 2.0 g of product described in Example 2 and 5 ml of mesyl chloride in 20 ml of N-methylpyrrolidone was heated for 1.5 h at 100° C. After cooling, water was added and the solution was extracted with ether. The solvent was evaporated in vacuo and the residue was crystallized from 1-propanol. Yield 0.14 g, m.p. 181°–184° C.

EXAMPLE 43

N-(1-Adamantyl)-3,4-diacetoxy-5-nitrobenzamide

A solution containing 0.85 g of 3,4-diacetoxy-5-nitrobenzoic acid and 0.32 ml of thionyl chloride and a catalytic amount of N,N-dimethylformamide in 10 ml of toluene was heated for 1 h at 80° C. The solvent was evaporated in vacuo and the residue was dissolved in 5 ml of dichloromethane and added to a mixture containing 0.56 g of 1-aminoadamantane hydrochloride and 0.94 ml of triethylamine in 10 ml of dichloromethane and stirred for 15 min at 0° C. and then 15 min at 20° C. Water was added to the reaction mixture and dichloromethane phase was separated. The solvent was evaporated in vacuo yielding yellow viscous oil 1.2 g (100%).

EXAMPLE 44

N-(1-Adamantyl)-3,4-dihydroxy-5-nitrobenzamide

A solution containing 1.2 g of the product obtained in Example 43 and a catalytic amount of sulfuric acid in 10 ml of methanol was refluxed for 3 h. 20 ml of water was added and on cooling 0.85 g (89.5%) of the desired product was crystallized, m.p. 207°614 208° C.

EXAMPLE 45

4-Cyclohexylcarbonyl-1-(3,4-diacetoxy-5-nitrobenzoyl)piperidine

The procedure described in Example 43 was repeated using 0.58 g of cyclohexylcarbonylpiperidine and 0.38 ml 2,6-lutidine instead of 1-aminoadamantane hydrochloride and triethylamine respectively. Yield 1.2 g (87%), a viscous yellow oil.

EXAMPLE 46

4-Cyclohexylcarbonyl-1-(3,4-dihydroxy-5-nitrobenzoyl)piperidine

The procedure described in Example 44 was repeated using 1.2 g of the product obtained in Example 45. Yield 0.5 g (50%), m.p. 155°–165° C.

EXAMPLE 47

N-Benzyl-3,4-diacetoxy-5-nitrobenzamide

0.75 g of 3,4-diacetoxy-5-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was dissolved in 5 ml of dichloromethane and added to a solution containig 0.27 ml of benzylamine and 0.5 ml of 2,6-lutidine in 7 ml of dichloromethane. Yield 0.95 g (96%), a viscous oil.

EXAMPLE 48

N-Benzyl-3,4-dihydroxy-5-nitrobenzamide

The procedure described in Example 44 was repeated using 0.95 g of the product obtained in Example 47. Yield 0.5 g (68%), m.p. 185°–189° C.

EXAMPLE 49

N-(1-Adamantyl)-3,4-cyclohexylidenedioxy-6-nitrobenzamide

2 g of 3,4-cyclohexylidenedioxy-6-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was added to a solution containing 1.1 g of 1-aminoadamantane and 1.1 ml of triethylamine in 15 ml of dichloromethane. Yield 2.9 g (98%), a viscous oil.

EXAMPLE 50

N-(1-Adamantyl)-3,.4-dihydroxy-6-nitrobenzamide

A solution containing 0.5 g of the product obtained in Example 49 and 0.09 ml of methanesulfonic acid in 8 ml of 98% formic acid was heated for 15 min at 60° C. The solvent was evaporated in vacuo and water was added to the residue. Yield 0.35 g (88%), m.p. 250°–255° C.

EXAMPLE 51

N-(4-Morpholinoethyl)-3,4-cyclohexylidenedioxy-6nitrobenzamide

2.0 g of 3,4-cyclohexylidenedioxy-6-nitrobenzoic acid was converted into the corresponding acid chloride like described in Example 43. It was added to a solution containing 0.9 ml of 4-(2-aminoethyl)morpholine and 1.1 ml of triethylamine in 15 ml of dichloromethane. Yield 2.5 g (89%), a viscous oil.

EXAMPLE 52

N-(4-Morpholine ethyl)-3,4-dihydroxy-6-nitrobenzamide hydromesylate

The procedure described in Example 50 was repeated using 1.95 g of the product obtained in Example 51. Yield 0.8 g (40%), viscous oil. The ^{1}H-NMR-spectrum was in accordance with the alleged structure.

EXAMPLE 53

N-(1-Adamantyl)-3,4-diacetoxy-5-chlorobenzamide

0.7 g of 3,4-diacetoxy-5-chlorobenzoic acid was converted to the corresponding acid chloride and the procedure described in Example 43 was repeated. Yield 1.0 g (95%), a viscous oil.

EXAMPLE 54

N-(1-Adamantyl)-3,4-dihydroxy-5-chlorobenzamide

The product of Example 53 was deacetylated like described in Example 44. Yield 0.6 g (78%), m.p. 244°–247° C.

EXAMPLE 55

N-(1-Adamantyl)-3,4-cyclohexylidenedioxy-6-chlorobenzamide

0.8 g of 3,4-cyclohexylidenedioxy-6-chlorobenzoic acid was converted to the corresponding acid chloride and the procedure described in Example 43 was repeated. Yield 1.0 g (83%), viscous oil.

EXAMPLE 56

N-(1-Adamantyl)-3,4-dihydroxy-6-chlorobenzamide

1.0 g of the product obtained in Example 55 was treated with methanesulfonic acid in formic acid as described in Example 50. Yield 0.65 g (81%), m.p. 225°–230° C.

EXAMPLE 57

N-(1-Adamantyl)-3,4-diacetoxy-5-cyanobenzamide

0.6 g of 3,4-diacetoxy-5-cyanobenzoic acid was converted to the corresponding acid chloride and the procedure described in Example 43 was repeated. Yield 0.75 g (88%), viscous oil.

EXAMPLE 58

N-(1-Adamantyl)-3,4-dihydroxy-5-cyanobenzamide

0.75 g of the above product was deacetylated as described in Example 44. Yield 0.5 g (89%), m.p. 253°–255° C.

EXAMPLE 59

1-Butyl-3,4-dihydroxy-5-cyanobenzoate

A solution containing 0.5 g of 3,4-dihydroxy-5-cyanobenzoic acid in 10 ml of 1-butanol was saturated with gaseous hydrogen chloride at 0° C. The solution was then heated for 3 h at 100° C. The solvent was evaporated in vacuo and dichloromethane was added to the residue. The formed crystals were filtered. Yield 0.19 g (30%), m.p. 135°–140° C.

EXAMPLE 60

ω-(2-Methylpiperidyl)-3,4-dimethoxy-6-cyanopropionanilide

A mixture containing 2.68 g of ω-chloro-3,4-dimethoxy-6cyanopropionanilide, 1.5 g of 2-methylpiperidine, 1.4 g of CaO and a catalytic amount of potassium iodide in 15 ml of toluene was heated for 18 h at 100° C. The solution was filtered, washed with water and evaporated in vacuo. The residue was treated with petro-

leum ether and filtered. Yield 2.79 g (84%), m.p. 126°–127° C.

EXAMPLE 61

ω-(1-Adamantylamino)-3,4-dimethoxy-6-cyanopropionanilide

A mixture containing 3.0 g of ω-chloro-3,4-dimethoxy-6cyanopropionanilide, 2.3 g of 1-aminoadamantane hydrochloride, 4.6 g of potassium carbonate and a catalytic amount of potassium iodide in 15 ml of toluene was heated while stirring for 6 h at 100° C. The solution was filtered and the solvent evaporated in vacuo. water was added to the residue and the product was filtered. Yield 3.4 g (74%), m.p. 137°–140° C.

EXAMPLE 62

1-(3,4-Cyclohexylidenedioxy-6-nitrobenzoyl)-4-cyclohexylcarbonylpiperidine

0.5 g of 3,4-cyclohexylidenedioxy-6-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was added to a solution containing 0.35 g of 4-cyclohexylcarbonylpiperidine and 0.2 g of triethylamine in 30 ml of dichloromethane. Yield 0.7 g (85%), m.p. 270° C.

EXAMPLE 63

1-(3,4-Dihydroxy-6-nitrobenzyl)-4-cyclohexylcarbonylpiperidine

0.48 g of the above product was treated with methanesulfonic acid in formic acid as described in Example 50. Yield 0.3 g (75%), m.p. 240° C.

EXAMPLE 64

1-(3,4-Cyclohexylidenedioxy-6-nitrobenzoyl)-4-(1-piperidyl)piperidine

The procedure described in Example 62 was repeated using 0.3 g of 4-(1-piperidyl)piperidine instead of 4-cyclohexylcarbonylpiperidine. Yield 0.57 g (74%), m.p. 200° C.

EXAMPLE 65

Cyclohexyl-4-[1-(3,4-cyclohexylidenedioxy-6-nitrobenzoyl)piperidyl]carbinol

To a solution containing 0.5 g of the product obtained in Example 62 and 1.1 ml of 1N NaOH in 20 ml of methanol 0.1 g of sodium borohydride was added at room temperature. The solution was acidified with acetic acid and extracted with dichloromethane. The solvent was removed in reduced pressure and the residue treated with petroleum ether. Yield 0.45 g (90%), m.p. 155° C.

EXAMPLE 66

1-(3,4-Dihydroxy-6-nitrobenzoyl)-4-(1-piperidyl)piperidine hydromesylate

0.3 g of the product obtained in Example 64 was treated with methanesulfonic acid in formic acid as described in Example 50. Yield 0.26 g (84%), m.p. 290° C.

EXAMPLE 67

1-(3,4-Diacetoxy-6-nitrobenzoyl)-4-cyclohexylcarbonylpiperidine

0.5 g of the product obtained in Example 63 was heated in 10 ml of acetic anhydride for 1 h at 40° C. Ice-water was added and the product was filtered. Yield 0.5 g (87%), m.p. 160°–165° C.

EXAMPLE 68

N-Methyl-N-propargyl-3,4-cyclohexylidenedioxy-6nitrobenzamide

0.5 g of 3,4-cyclohexylidenedioxy-6-nitrobenzoic acid was converted to the corresponding acid chloride and added to a solution containing 0.12 g methylpropargylamine and 0.18 g of triethylamine in 20 ml of dichloromethane. Yield 0.3 g (50%), m.p. 50°–55° C.

EXAMPLE 69

1-(3,4-Dimethoxy-6-nitrobenzoyl)-4-cyclohexylcarbonyl piperidine

10.3 g of 3,4-dimethoxy-6-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was added to a solution containing 8.83 g of 4-cyclohexylcarbonylpiperidine and 4.58 g of triethylamine in 300 ml of dichloromethane. Yield 16.4 g (90%), m.p. 120°–125° C.

EXAMPLE 70

1-(3,4-Dihydroxy-6-nitrobenzoyl)-4-cyclohexylcarbonyl-piperidine

A solution containing 0.81 g of the above compound in 12 ml of 1 molar BBr_3—CH_2Cl_2 was stirred over night at 20° C. Water was added and the product was filtered. Yield 0.5 g (67%), m.p. 240° C.

EXAMPLE 71

Cyclohexyl-4-[1-(3,4-dimethoxy-6-nitrobenzoyl)-piperidyl]carbinol

2.03 g of the product obtained in Example 69 was reduced with sodium borohydride as described in Excample 65. Yield 1.89 g (93%), m.p. 145°–150° C.

EXAMPLE 72

3-(3-Ethoxycarbonylmethylcarbamoyloxy-4-hydroxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

1.5 g of ethyl isocyanatoacetate was added to a solution containing 0.54 g of the product obtained in Example 8 in 10 ml of tetrahydrofuran and the solution was stirred for 3 days at 20° C. The solvent was evaporated in reduced pressure and the raw product was purified in a silica gel column using toluene-dioxane-acetic acid (8:1:1) as an eluent. Crystallization from acetone-petroleum ether yielded 0.13 g (17%) of the desired product desired, m.p 155°–158° C.

EXAMPLE 73

3-(3,4-Methylenedioxy-6-nitrophenyl)-1-phenylprop-2-en-1-one

The procedure described in Example 8 was repeated by using 1.95 g of 6-nitropiperonal and 2.10 g of 3′,4′,5′-trimethoxyacetophenone in 30 ml of methanol. Yield 0.88 (24%), m.p. 157°–159° C.

EXAMPLE 74

3-(4-Hydroxy-3-methoxy-5-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

The procedure described in Example 8 was repeated by using 2.0 g of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde and 2.1 g of 3′,4′,5′-trimethoxyacetophenone. Yield 2.2 g (57%), m.p. 123°–125° C.

EXAMPLE 75

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(2-carboxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.64 g of 2'-carboxyacetophenone. Yield 0.36 g (11%), m.p. 178-180° C.

EXAMPLE 76

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(4-nitrophenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.65 g of 4'-nitroacetophenone. Yield 1.25 g (38%), m.p. 255°–256° C.

EXAMPLE 77

3-(3-methoxy-4-hydroxy-5-trifluoromethylphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

The procedure described in Example 8 was repeated using 2.2 g of 3-methoxy-4-hydroxy-5-trifluoromethylbenzaldehyde and 2.1 g of 3',4',5'-trimethoxyacetophenone Yield 2 6 g (61%), m,p, 190°–192° C.

EXAMPLE 78

4-(3,4-Dimethoxy-5-methylsulfonylphenyl)-3-methyl-but-3-en-2-one

The procedure described in Example 8 was repeated using 2.44 g of 3,4-dimethoxy-5-methylsulfonylbenzaldehyde and 1.0 g of 2-butanone. Yield 2.0 g (63%), viscous oil.

EXAMPLE 79

2,5-Bis-(3,4-dihydroxy-5-nitrobenzylidene)cyclopentanone

The procedure described in Example 8 was repeated using 5.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 2.0 g of cyclopentanone. Yield 4.4 g (78%), m.p. 300° C. (decomp.).

EXAMPLE 80

1-Phenyl-3-(3-stearoyloxy-4-hydroxy-5-nitrophenyl)-prop-2-en-1-one

A solution containing 2.0 g of the product obtained in Example 8 and 10.0 g of stearoyl chloride in 10 ml of dioxane was stirred and heated for 18 h at 90° C. After cooling petroleum ether was added and the product was filtered. Recrystallization from dichloromethane-petroleum ether yielded 0.64 g (17%) of the desired product desired, m.p. 112°–118° C.

EXAMPLE 81

Ethyl 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylate

The procedure described in Example 4 was repeated using 1.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde, 0.9 g of ethyl cyanoacetate and 0.15 g of ammonium acetate in 10 ml of ethanol. Yield 0.87 g (57%), m.p. 205°–210° C.

EXAMPLE 82

Methyl 3-(3,4-dihydroxy-5-nitrobenzylidine)-4-ketopentanoate

A solution containing 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.1 g of levulinic acid in 10 ml of methanol was saturated with gaseous hydrogen chloride. The mixture was refluxed for 20 h after which water was added and the solution was extracted with ether. The solvent was evaporated in reduced pressure and the residue crystallized from ether-petroleum ether. Yield 0.54 g (20%), m.p. 142°–150° C.

EXAMPLE 83

3,4-Dihydroxy-5-nitrobenzylmalonitrile

1.5 g of sodium borohydride was added to a suspension containing 3.7 g of the product obtained in Example 5 in 10 ml of water at room temperature. The solution was stirred for 2 h more, acidified with hydrochloric acid and extracted with ether. The solvent was evaporated in vacuo and the residue crystallized from methanol-isopropanol. Yield 1.1 g (30%), m.p. 211°–215° C.

EXAMPLE 84

Ethyl 3,4-dihydroxy-5-nitrobenzylcyanoacetate

The procedure described in Excample 83 was repeated using 2.78 g of the product obtained in Example 81. Yield 0.98 g (35%), yellow viscous oil.

EXAMPLE 85

1-Phenyl-3-(3-methoxy-4-hydroxy-5-trifluoromethyl-phenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.7 g of 3-methoxy-4-hydroxy-5-trifluoromethylbenzaldehyde and 1.0 g of acetophenone. Yield 1.1 g (45%), m.p. 166°–168° C.

EXAMPLE 86

1-Phenyl-3-(3,4-dihydroxy-5-trifluoromethylphenyl)-prop-2-en-1-one

To a solution containing 0.32 g of the above product obtained in Example 85 in 10 ml of dichloromethane 3 ml of 1 molar BBr3-CH2C12 was added. The mixture was stirred for 20 min at room temperature, acidified with 10 ml 2 N hydrochloric acid and extracted with dichloromethane. The solvent was evaporated in reduced pressure and the residue crystallized from acetone-dichloromethane. Yield 0.07 g (23%), m.p. 196°–201° C.

EXAMPLE 87

3,4-Dihydroxy-5-sulfonamidobenzaldehyde

A solution containing 1.89 g of 2,3-dihydroxybenzenesulfonamide and 1.4 g of hexamethylenetetramine in 20 ml of trifluoroacetic acid was refluxed for 2 h. The solvent was evaporated in vacuo, water was added to the residue and the product was filtered. Yield 0.78 g (35%).

EXAMPLE 88

2-Methoxy-6-trifluoromethylphenol

A solution containing 160 ml of 1.6 molar butyllithium in hexane, 300 ml of tetrahydrofuran and 40 ml of N,N,N',N'-tetramethylethylenediamine was cooled to −78° C. and 43.3 g of 3-trifluoromethylanisole was added with stirring under nitrogen atmosphere. The solution was allowed to warm up to room temperature and cooled then again to −78° C. after which 35 ml of trimethyl borate was added. The solution was warmed up to 20° C. and 50 ml of conc. ammonia solution was

added. The solvents were evaporated in reduced pressure and to the residue 60 ml of 98–100% formic acid followed with 25 ml of 35% hydrogen peroxide were added. The solution was extracted with ether-petroleum ether (1:1). The organic phase was separated and the product was extracted with 2.5 N NaOH-solution. The aqueous phase was acidified with hydrochloric acid and the product was extracted in dichloromethane. The solvent was removed for the most part in vacuo after which petroleum ether was added. The crystalline product was filtered, yield 8.5 g (18%), m.p. 51°–53° C.

EXAMPLE 89

4-Hydroxy-3-methoxy-5-trifluoromethylbenzaldehyde

A solution containing 1.9 g of 2-methoxy-6-trifluoromethylphenol and 1.4 g of hexamethylenetetramine in 20 ml of trifluoroacetic acid was refluxed for 1 h. The solvent was removed in reduced pressure, 50 ml of 1 N hydrochloric acid was added to the residue and the solution was extracted with dichloromethane. Most part of the solvent was evaporated in vacuo and petroleum ether was added, whereupon the product crystallized. Yield 0.7 g (32%), m.p. 151°–152° C.

EXAMPLE 90

3,4-Dimethoxy-5-cyanobenzaldehyde

A mixture containing 2.5 g of 3,4-dimethoxy-5-bromobenzaldehyde and 1.0 g of cuprous cyanide in N-methylpyrrolidone was refluxed for 2 h. Water was added and the solution was extracted with dichloromethane. The solvent was evaporated in vacuo. Yield 1.55 g (81%), m.p. 109°–112° C.

EXAMPLE 91

3,4-Dihydroxy-5-cyanobenzaldehyde

A solution containing 0.96 g of the above product in 15 ml of 1 molar BBr_3—CH_2Cl_2-solution was stirred for 4 h at room temperature under nitrogen. 15 ml of 1 N hydrochloric acid was added and the dichloromethane phase was separated. The solvent was evaporated in vacuo. Yield 0.61 g (75%), m.p. 210°–215° C.

EXAMPLE 92

1,2-Dimethoxy-3-methylsulfonylbenzene

To a solution containing 3.68 g of 2,3-dimethoxythioanisole in 50 ml of dichloromethane 3.6 g of 3-chloroperoxybenzoic acid was added with stirring. Stirring was continued for 18 h more at room temperature. 30 ml of 1 N NaOH-solution was added, dichloromethane phase was separated and the solvent evaporated in vacuo. Yield 4.51 g (91%), a viscous oil.

EXAMPLE 93

3,4-Dimethoxy-5-methylsulfonylbenzaldehyde

The procedure described in Example 89 was repeated using 2.16 g of 2 hexamethylenetetramine. Yield 0.97 g (45%), a viscous oil.

EXAMPLE 94

3,4-Dihydroxy-5-methylsulfonylbenzaldehyde

A solution containing 0.5 g of the above product and 5 ml of 48% hydrobromic acid in 5 ml of acetic acid was refluxed for 8 h. Water was added and the solution was extracted with dichloromethane. The solvent was evaporated in vacuo. Yield 0.3 g (68%), a viscous oil.

EXAMPLE 95

3,4-Dihydroxy-5-cyanobenzaldehyde

A solution containing 1.35 g of 2,3-dihydroxybenzonitrile and 1.4 g of hexamethylene tetramine in 20 ml of trifluoroacetic acid was refluxed for 1.5 h. Water was added and the product was filtered. Yield 0.9 g (55%), m.p. 211°–215° C.

EXAMPLE 96

3-(3,4-Dihydroxy-5-trifluoromethylphenyl)-1-phenyl-prop-2-en-1-one

The procedure described in Example 8 was repeated using 2.06 g of 3,4-dihydroxy-5-trifluoromethylbenzaldehyde and 1.20 g of acetophenone. Yield 2.19 g (71%), m.p. 196°–210° C.

EXAMPLE 97

3,4-Dihydroxy-5-trifluoromethylbenzaldehyde

A solution containing 2.2 g of 4-hydroxy-3-methoxy-5-trifluoromethylbenzaldehyde in 65 ml of 1 molar BBr_3 in dichloromethane was stirred for 2 h at room temperature. Hydrochloric acid was added and the organic phase was separated. The solvent was evaporated in vacuo. Yield 1.4 g (68%), m.p. 188°–192° C.

EXAMPLE 98

2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide

A solution containing 1.3 g of 3,4-dihydroxy-5-nitrobenzaldehyde, 0.73 g of cyanoacetamide and catalytic amount of piperidine acetate in 40 ml of dry ethanol was refluxed over night. The solvent was evaporated in vacuo and the residue was recrystallized water-DMF. Yield 0.84 g (48%), m.p. 296°–298° C.

EXAMPLE 99

N,N-Dimethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide

A solution containing 1.83 g of 3,4-dihydroxy-5-nitrobenzaidehyde, 1.2 g of N,N-dimethylcyanoacetamide and catalytic amount of piperidine acetate in 40 ml of dry ethanol was refluxed over night. Yield 1.1 g (40%), m.p. 183°–185° C.

EXAMPLE 100

N,N-Diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl-)acrylamide

The procedure described in Example 99 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.5 g of N,N-diethylcyanoacetamide. Yield 2.23 g (73%), m.p. 153°–156° C.

EXAMPLE 101

N-Isopropyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl-)acrylamide

The procedure described in Example 99 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.3 g of N-isopropylcyanoacetamide. Yield 1.46 g (50%), m.p. 243°–245° C.

EXAMPLE 102

N'-Methyl-N''-[2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acryl]piperazine

The procedure described in Example 99 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.7 g of N'-methyl-N''-cyanoacetylpiperazine. Yield 2.16 g (65%), m.p. 65° C. (decomp.).

EXAMPLE 103

3-(3,4-Dihydroxy-5-trifluoromethylbenzylidene)-2,4-pentanedlone

The procedure described in Example 7 was repeated using 2.06 g of 3,4-dihydroxy-5-trifluoromethyl-benzaldehyde and 1.00 g of 2,4-pentanedione. Yield 1.39 g (45%), m.p. 98°–205° C.

EXAMPLE 104

3,4-Dihydroxy-5-nitrobenzylalcohol

To a solution containing 6.0 g of sodium borohydride in 50 ml of water 9.15 g of 3,4-dihydroxy-5-nitrobenzaldehyde was gradually added with stirring at room temperature. The mixture was stirred for 1 h more after which it was acidified with hydrochloric acid. The solution was filtered to remove tarry impurities and extracted 4 times with ether. The ether extract was dried over anhydrous sodium sulfate, filtered and concentrated to a volume of about 100 ml.

The crystalline solid was filtered. Yield 6.0 g (65%), m.p. 100° C. (decomp.).

EXAMPLE 105

3,4-Dihydroxy-5-nitrobenzyl-2-methoxyethyl ether

A solution of 1.0 g of 3,4-dihydroxy-5-nitrobenzylalcohol in 5.0 ml of 2-methoxyethanol was refluxed for 1 h. The solvent was evaporated in vacuo and the residue was triturated with isopropanol. Yield 0.4 g (30%), m.p. 154°–157° C.

EXAMPLE 106

3,4-Dihydroxy-5-nitrobenzylthioacetic acid

A solution containing 1.0 g of 3,4-dihydroxy-5-nitrobenzylalcohol in 5.0 g of thioglycolic acid was stirred for 1.5 h at 120° C. 25 ml of water was added and product was filtered and washed with water. Yield 0.25 g (19%), m.p. 91°–93° C.

EXAMPLE 107

2-(3,4-Dihydroxy-5-nitrobenzyl)pyrrole

A solution containing 1.0 g of 3,4-dihydroxy-5-nitrobenzyl alcohol and 5.0 ml of pyrrole in 3.0 ml of dioxane was heated for 5 h at 100° C. Water was added and the solution was extracted with dichloromethane. The solvent was evaporated and the residue was purified in a silicagel column using toluene-acetic acid-dioxane (18:1:1) mixture as an eluent. Yield 0.42 g (33%), m.p. 115°–118° C.

EXAMPLE 108

2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)propanol

To a solution containing 0.85 g of ethyl 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylate (Example 81) in 70 ml of dry ethanol 0.3 g of sodium borohydride was gradually added. The solution was stirred for 0.5 h at room temperature, acidified with hydrochloric acid and extracted with ethyl acetate. The solvent was evaporated yielding 0.55 g (75%) of yellow crystals, m.p. 149°–152° C.

EXAMPLE 109

3-Nitrocatechol

To a solution containing 2.5 g of catechol in 125 ml of ether 1.0 ml of conc. nitric acid (d-1.52) was gradually added. The solution was stirred over night at room temperature and washed with water. The solvent was evaporated and the residue was treated with boiling petroleum ether (b.p. 60°–80° C). The insoluble 4-nitrocatechol was filtered and the filtrate concentrated in vacuo. After cooling the 3-nitrocatechol was filtered. Yield 0.85 g (24%), m.p. 82°–85° C.

EXAMPLE 110

3,5-Dinitrocatechol

To a solution containing 50.0 g of catechol diacetate in 250 ml of acetic acid 125 ml of nitric acid (d-1.42) was gradually added at 50° C. The solution was stirred for 1.5 h more at 50° C. and poured then to crushed ice. The product was filtered, washed with water and dissolved in 500 ml of methanol containing 1.0 ml of conc. sulfuric acid. The solution was refluxed for 2.5 h. Methanol was distilled off to a great ,extend and 100 ml of water was added. The remaining methanol was evaporated in vacuo whereupon the product was crystallized. Yield 20.9 g (40.4%), m.p. 168°–170° C.

EXAMPLE 111

3,4-Dihydroxy-5-nitrobenzaldehyde

A solution containing 8.0 kg of 5-nitrovanillin and 8.7 kg of acetic acid in 35 kg of conc. hydrobromic acid was refluxed for 20 h. 0.6 kg of charcoal was added and the mixture was filtered. 32 kg of water was added with stirring and the solution was cooled to −10° C. and stirring was continued for 2 h more. The crystalline product was filtered and washed with water. Yield 5.66 kg (80%), m.p. 135°–137° C.

EXAMPLE 112

3,4-Dihydroxy-5-nitrobenzonitrile

A solution containing 0.92 g of 3,4-dihydroxy-5-nitrobenzaidehyde. and 0.49 g of hydroxylamine hydrochloride in 5.0 ml of formic acid was refluxed for 1 h. 50 ml of water was added and the product was filtered and washed with water. Yield 0.3 g (33%), m.p. 175°–178° C.

EXAMPLE 113

4-Chloro-6-nitrocatechol

A mixture containing 1.0 g of 4-chloro-3-methoxy-6nitrophenol in 20 ml of conc. hydrobromic acid was refluxed for 2 h. After cooling the product was filtered and washed with water. Yield 0.6 g (65%), m.p. 108°–111° C.

EXAMPLE 114

4,5-Dihydroxyisophthalaldehyde

To a suspension containing 1.8 g of 4-hydroxy-5-methoxyisophthalaldehyde in 20 ml of dichloromethane was added 35 ml of 1 molar PBr_3 in dichloromethane. The mixture was allowed to stand over night at room temperature and poured into ice-water, Dichloromethane was evaporated in vacuo. After cooling the product

was filtered and washed with wash. Yield 0.94 g (57%), m.p. 192°–195° C.

EXAMPLE 115

3,4-Dihydroxy-5-cyanobenzoic acid

To a solution containing 2.3 g of 4-acetoxy-3-cyano-5-methoxybenzoic acid in 10 ml of dichloromethane 40 ml of 1 molar PBr_3 in dichloromethane was added. The mixture was stirred ever night at room temperature. The solvent was evaporated in vacuo and to the residue ice-water was added. The product was filtered and washed with water. Yield 1.25 g (74%), m.p. 269°–271° C.

EXAMPLE 116

3,4-Dihydroxy-5-nitrophenylalanine hydrobromide

A solution containing 1.2 g of 4-hydroxy-3-methoxy-5-nitrophenylalanine hydrosulfate in 10 ml of conc. hydrobromic acid was refluxed for 2 h. The solution was concentrated in vacuo and allowed to stand over night in a refrigerator. The product was filtered and washed with hydrobromic acid and dried. Yield 0.25 g, m.p. 170° C. (decomp.).

EXAMPLE 117

3,5-Dicyanocatechol

A solution containing 0.83 g of 3,5-diformylcatechol and 0.90 g of hydroxylamine hydrochloride in 30 ml of formic acid was refluxed for 16 hours. Formic acid was evaporated in vacuo and water was added to the residue. The solution was extracted with ether. The solvent was evaporated and the residue was crystallized from ethanol-water. Yield 0.28 g (43%), m.p. 300° C. (decomp.).

EXAMPLE 118

N,N-diethyl-5-chloro-2,3-dihydroxybenzenesulfonamide

To a solution containing 0.7 g of N,N-diethyl-5-chloro-3,4-dimethoxybenzenesulfonamide in 10 ml of dichloromethane 9.0 ml of 1 molar BBr_3 in dichloromethane was added. The solution was stirred overnight at room temperature. Water and hydrochloric acid were added and the mixture was extracted with dichloromethane. The solvent was evaporated. Yield 0.3 g (47%), m.p. 62°–64° C.

EXAMPLE 119

4-Chloro-6-methylsulfonylcatechol

The procedure described in Example 118 was repeated using 4-chloro-2-methoxy-6-methylsulfonylphenol. Yield 50%, m.p. 142°–145° C.

EXAMPLE 120

4-Nitro-6-methylsulfonylcatechol

The procedure described in Example 118 was repeated using 2-methoxy-4-nitro-6-methylsulfonylphenol. Yield 21%, m.p. 221°–224° C.

EXAMPLE 121

3,4-Dihydroxy-5-methylsulfonylbenzaldehyde

The procedure described in Example 118 was repeated using 4-hydroxy-3-methoxy-5-methylsulfonylbenzaldehyde- Yield 17%, m.p. 169°–171° C.

EXAMPLE 122

N-(3-hydroxypropyl)-3,4-dihydroxy-5-nitrobenzamide

The procedures described in Examples 43 and 44 were repeated using 3,4-diacetoxy-5-nitrobenzoic acid and 3-aminopropan-1-ol. Yield 85%, m.p. 160°–163° C.

EXAMPLE 123

Neopentyl
2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylate

The procedure described in Example 4 was repeated using 3,4-dihydroxy-5-nitrobenzaldehyde and neopentyl cyanoacetate. Yield 67%, m.p. 173°–179° C.

EXAMPLE 124

N-(3-hydroxypropyl)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide

The procedure described in Example 99 was repeated using N-(3-hydroxypropyl)cyanoacetamide and 3,4-dihydroxy-5-nitrobenzaldehyde. Yield 52%, m.p. 223°–228° C.

EXAMPLE 125

2,3-Dihydroxy-5-nitrobenzonitrile

The procedure described in Example 118 was repeated using 2-hydroxy-3-methoxy-5-nitrobenzonitrile. Yield 45%.

EXAMPLE 126

3,5-Dicyanocatechol

To a solution containing 2,4-dicyano-6-methoxyphenol in 20 ml of dichloromethane 20 ml of 1 molar solution of BBr_3 in dichloromethane was added. The solution was stirred overnight at room temperature. Water and hydrochloric acid were added and the mixture was extracted with dichloromethane. The solvent was evaporated. Yield 0.8 g (50%), m.p. 300° C. (decomp.).

EXAMPLE 127

1,2-Diacetoxy-3,5-dinitrobenzene

A catalytic amount of concentrated sulfuric acid was added to a solution containing 2.0 g of 3,5-dinitrocatechol in 15 ml of acetanhydride and the solution was mixed for ½ hours in 50°–60° C. Ice water was added to the rection mixture and the solution was mixed in 0° C. whereby the product was crystallized. The product was filtered and washed with water and dried. Yield 2.75 g (97%), m.p. 115°–117° C.

EXAMPLE 128

1,2-Dipropionyloxy-3,5-dinitrobenzene

The procedure of Example 127 was repeated using propionic acid anhydride instead of acetanhydride. Yield 2,8 g (90%), m.p. 72°–73° C.

EXAMPLE 129

1,2-Dibutyryloxy-3,5-dinitrobenzene

The procedure described in Example 127 was repeated using butyrylanhydride instead of acetanhydride. Yield 70%, m.p. 65°–60° C.

EXAMPLE 130

2-Butanoyloxy-4,6-dinitrophenol

8.7 ml of nitric acid (d-1.42) was added stirring and cooling to a solution containing 2.4 g of catechol dibutyrate in 25 ml of acetic acid. The solution was stirred for further ½ hours and ice water was added thereto. The product was filtered and washed with water. Yield 1.85 g (53%), m.p. 65°–70° C.

EXAMPLE 131

2-Pivaloyloxy-4,6-dinitrophenol

6.7 ml of nitric acid (d-1.42) was added stirring and cooling (in 20°–25° C.) to a solution containing 1.94 g of catechol monopivaloate in 20 ml of acetic acid. The solution was stirred for ½ hours in 50° C. Ice water was added and the product was filtered and washed with water. Yield 1.75 g (62.5%). m.p. 132°–135° C.

EXAMPLE 132

2-Benzoyloxy-4,6-dinitrophenol

A mixture containing 2.0 g of 3,5-dinitrocatechol in 5 ml of benzoylchloride was cooked for 4 hours in 100° C. When cooled petroleum ether (b.p. 40° C.) was added and the product was filtered and washed with petroleum ether. The raw product was crystallized from ethanol. Yield 2.5 g (82%), m.p. 150°–152° C.

EXAMPLE 133

3-(4-Hydroxy-5-nitro-3-pivaloyloxybenzylidene)-2,4-pentanedione

A mixture containing 2.0 g of the product obtained according to Example 7 in 5 ml of pivaloylchloride was heated for 4 hours in 100° C. The excess pivaloylchloride was evaporated away in reduced pressure and ether was added to the residue. The product was filtered and washed with ether. Yield 1.41 g (58%), m.p. 143°–145° C.

EXAMPLE 134

2-(2,6-Dimethylbenzoyloxy)-4,6-dinitrophenol

A mixture containing 2.0 g of 3,5-dinitrocatechol in 5 ml of 2,6-dimethylbenzoylchloride was heated for 20 hours in 100° C. The excess 2,6-dimethylbenzoylchloride was removed in high vacuum. The residue was purified in silicagel column. Yield 1.5 g (45%), yellow viscous oil, which was crystallized from petroleum ether, m.p. 163°–165° C.

EXAMPLE 135

2-(2,6-Dimethoxybenzoyloxy)-4,6-dinitrophenol

The procedure of Example 134 was repeated using 2,6-dimethoxybenzoylchloride. Yield 1.3 g (36%), m.p. 217°–218° C.

EXAMPLE 136

2-(1-Methylcyclohexylcarbonyloxy)-4,6-dinitrophenol

The procedure of Example 134 was repeated using 1-methylcyclohanecarboxylic acid chloride. Yield 1.6 g (49%), yellow

EXAMPLE 137

1,2-Bis(2,6-dimethylbenzoyloxy)-3,5-dinitrobenzene

The procedure of Example 134 was repeated using a temperature of 134° C. The product was crystallized from 50% ethanol. M.p. 175°–178° C. Yield 60%.

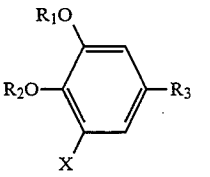
EXAMPLE 138

1,2-Bis(3-ethoxycarbonylpropionyloxy)-3,5-dinitrobenzene

A solution containing 1 g of 3,5-dinitrocathecol in 2,5 ml of ethyl ester chloride of succinic acid was heated for 3 h in 100° C. The product was purified in silicagel column. M.p. 60°–63° C.

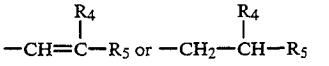
What is claimed is:

1. A compound according to formula I



I

wherein R_1 and R_2 independently represent hydrogen, carbamoyl which is substituted by an alkyl of 1 to 4 carbon atoms, alkylcarbonyl of 2 to 5 carbon atoms or phenyl carbonyl, X represents nitro or cyano and R_3 represents



wherein R_4 represents cyano or alkylcarbonyl of 2 to 5 carbon atoms and R_5 represents carbamoyl which is unsubstituted or substituted with alkyl of 1 to 8 carbon atoms or which is substituted with hydroxyalkyl of 1 to 8 carbon atoms or pharmaceutically acceptable esters and salts thereof.

2. The compound according to claim **1**, wherein R_4 is cyano and R_5 is carbamoyl which is unsubstituted or substituted with alkyl of 1 to 3 carbon atoms.

3. N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.

4. A compound selected from the group consisting of 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide, N,N-dimethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl-)acrylamide and N-isopropyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-acrylamide.

* * * * *

EXHIBIT B

US005135950A

United States Patent [19]

Pippuri et al.

[11] **Patent Number: 5,135,950**

[45] **Date of Patent: Aug. 4, 1992**

[54] **STABLE POLYMORPHIC FORM OF (E)-N,N-DIETHYL-2-CYANO-3-(3,4-DIHYDROXY-5-NITROPHENYL)ACRYLAMIDE AND THE PROCESS FOR ITS PREPARATION**

[75] Inventors: **Aino K. Pippuri**, Espoo; **Erkki J. Honkanen**, Vantaa; **Jorma V. Haarala**, Helsinki, all of Finland

[73] Assignee: **Orion-yhtymä Oy**, Espoo, Finland

[21] Appl. No.: **606,717**

[22] Filed: **Oct. 31, 1990**

[30] **Foreign Application Priority Data**

Nov. 3, 1989 [GB] United Kingdom 8924838.9

[51] **Int. Cl.**[5] **A61K 31/275**; C07C 255/07

[52] **U.S. Cl.** **514/521**; 558/401

[58] **Field of Search** 558/401; 514/521

[56] **References Cited**

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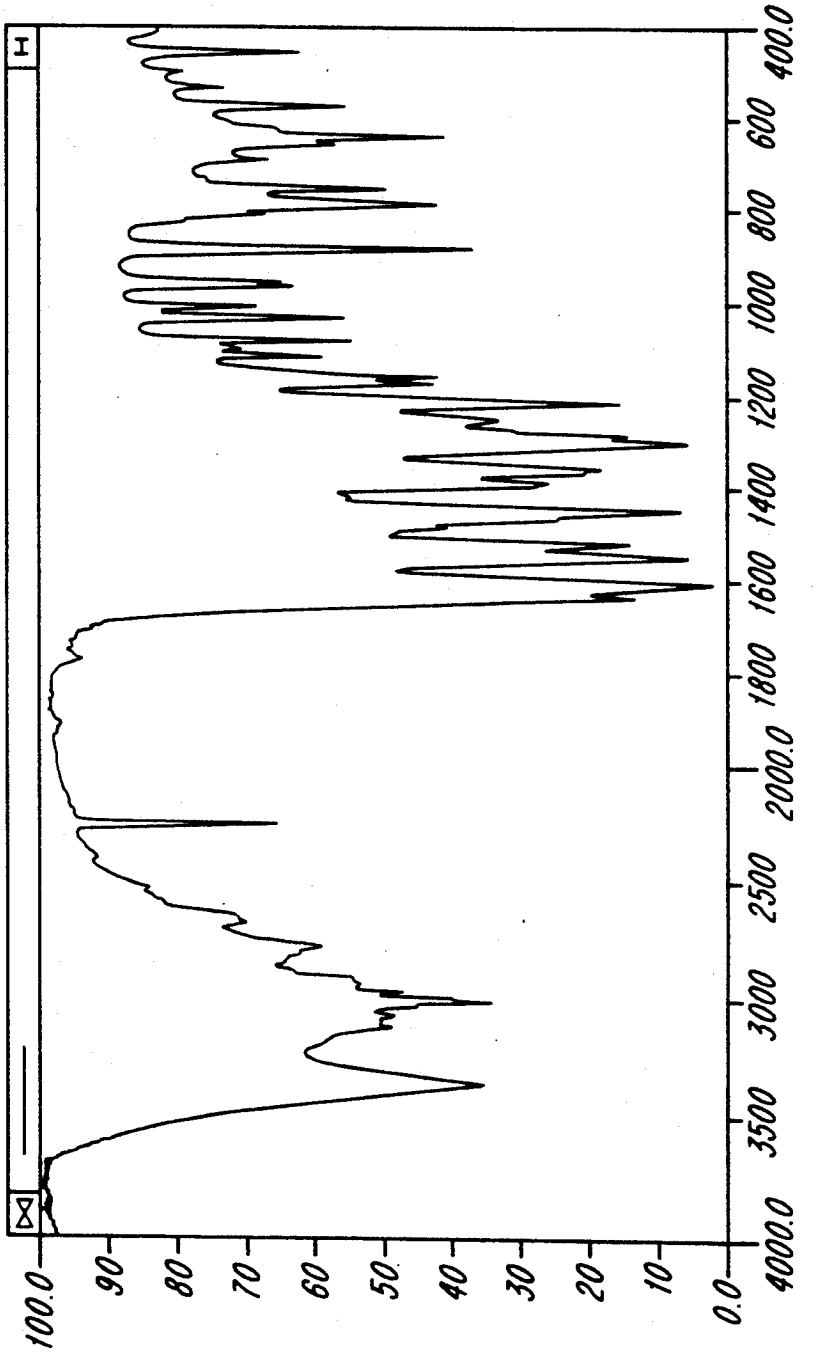
Primary Examiner—Joseph Paul Brust
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis

[57] **ABSTRACT**

Stable and crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitro-phenyl)acrylamide may be prepared by crystallizing crude synthesis product from lower aliphatic carboxylic acid such as formic or acetic acid with a catalytic amount of hydrochloric or hydrobromic acid added. The product is a potent inhibitor of catechol-O-methyl-transferase enzyme (COMT).

10 Claims, 2 Drawing Sheets

Fig. 1


100.0
90
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1000
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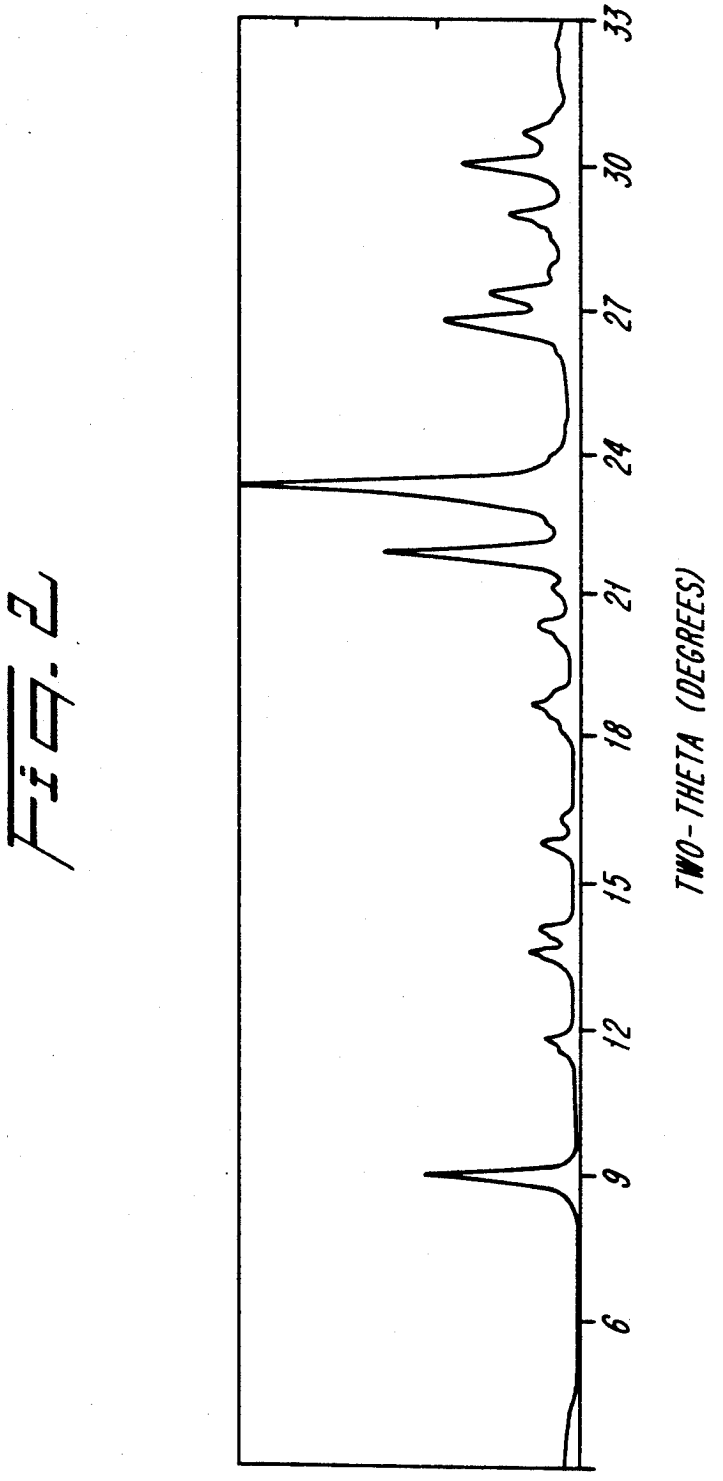
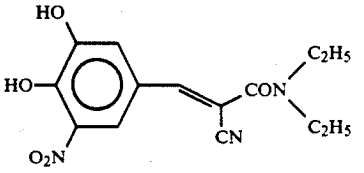


Fig. 2

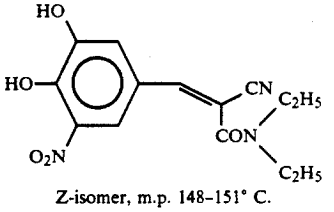
STABLE POLYMORPHIC FORM OF (E)-N,N-DIETHYL-2-CYANO-3-(3,4-DIHYDROXY-5-NITROPHENYL)ACRYLAMIDE AND THE PROCESS FOR ITS PREPARATION

The present invention relates to the stable and crystallographically essentially pure polymorphic form of N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide E-isomer, denoted (E)-N,N-diethyl -2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide A, and to a process for the preparation thereof.

N,N-Diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide described in British patent application No. 8727854 by the applicant is a potent inhibitor of catechol-O-methyl-transferase enzyme (COMT) and may be used pharmaceutically in the treatment of e.g., Parkinson's disease. This compound with a melting point of 153-156° C. has proven to be a mixture of two geometric isomers, E- and Z-isomers (70-80% E-isomer and 30-20% Z-isomer) having formulae:



E-isomer, m.p. 162–163° C.



Z-isomer, m.p. 148–151° C.

(E)-N,N-Diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide (I) may exist at least in two polymorphic forms A and B as shown by X-ray crystallography. The Z-isomer as well as the polymorphic form B of the E-isomer have been shown to be unstable. The Z-isomer is transformed readily into the E-isomer under the influence of heat or acids. Similarly the polymorphic form B of the E-isomer isomerizes slowly to the polymorphic form A on standing at room temperature. On recrystallization of the crude synthesis product from conventional solvents such as lower aliphatic alcohols, esters or hydrocarbons, e.g., ethanol, 2-propanol, ethyl acetate or toluene, a very complicated mixture of different geometric isomers and/or polymorphic forms are generally obtained which interfere with the characterization and standardization of the drug substance. The polymorphism and geometrical isomerism may also influence the bioavailability of the drug.

Surprisingly, it has now been observed that crystallographically essentially pure and stable polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide is obtained in good yield, when the crude product of synthesis is recrystallized from lower aliphatic carboxylic acid such as formic or acetic acid with a catalytic amount of hydrochloric or hydrobromic acid added. This method allows large scale production of homogenous and crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide independent of batch size or cooling rate.

"Crystallographically essentially pure" when used herein means the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide containing a maximum of 3% and preferably a maximum of 2% of other polymorphic forms or the Z-isomer.

"Lower aliphatic-carboxylic acid" means here aliphatic carboxylic acid having 1–2 carbon atoms. Examples are formic and acetic acid.

The polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide is characterized either by IR-spectrometry or X-ray crystallography. IR-spectrum of the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide is seen in FIG. 1 and the typical IR-absorption bands are presented in Table 1.

TABLE 1

Typical IR-absorption bands of the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide

Wave numbers (cm^{-1}) and the relative intensities of absorption bands	Assignment of the vibrational modes
3339 s	O—H stretching
3092 w	C—H stretching, aromatic and
3066 w	unsaturated
3039 w	
2981 w	C—H stretching,
2938 w	saturated
2217 m	CN stretching
1628 s	tertiary amide C=O stretching
1607 s	C=C stretching,
1580 sh	conjugated with C=O and aromatic ring; and C=C stretching, aromatic
1544 s	NO_2 asymmetric stretching
1512 m	C=C stretching, aromatic
1441 s	CH_2 bending; asymmetric CH_3 bending; C=C stretching, aromatic
1377 s	NO_2 symmetric stretching; OH bending
1298 s	C—O stretching
1281 sh	
1210 m	C—H bending,
1165 m	aromatic
1150 m	
800 sh	C—H out of plane
779 m	bending, aromatic
740 m	
Experimental	
Instrument:	Perkin-Elmer FTIR 1725X
Detector:	TGS
ordinate mode:	% T
Abscissa mode:	Wave numbers (cm^{-1})
Resolution:	4 cm^{-1}
Number of scans:	20
Phase:	KBr

s = strong; m = medium; w = weak; sh = shoulder

The X-ray powder diffraction patterns of the polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy -5-nitrophenyl)acrylamide are seen in FIG. 2 and the crystallographic data in Table 2.

TABLE 2

Crystallographic data of polymorphic form A

TABLE 2-continued

of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide
Peak positions (2θ), interplanar spacings (d) and relative peak intensities of the first 20 reflections.

No	2θ	d	Rel I (%)
1	3.680	23.9905	0.8
2	9.040	9.7745	49.7
3	11.840	7.4685	9.9
4	13.541	6.5339	11.1
5	14.060	6.2939	11.6
6	15.820	5.5974	7.6
7	16.320	5.4270	3.9
8	18.220	4.8651	4.6
9	18.459	4.8027	8.7
10	18.720	4.7363	13.6
11	18.940	4.6818	5.5
12	20.041	4.4270	5.0
13	20.380	4.3541	11.1
14	21.140	4.1993	3.5
15	21.939	4.0481	58.3
16	22.901	3.8802	13.8
17	23.340	3.8082	100.0
18	23.960	3.7110	3.3
19	24.480	3.6334	2.9
20	26.343	3.3805	3.6

Experimental

Instrument:	Siemens DSOO
Wavelength:	0.1541 nm (CuK_1)
Range:	30°–33° (2θ)
Power:	40 mA/40 kV
Time:	1°/min (0.02° step)

For the treatment of Parkinson's disease, the stable polymorphic compound of the present invention may be administered to a patient in need of such treatment along with levodopa. A peripheral decarboxylate (DDC) inhibitor, such as carbidopa or benserazide may be optionally present.

The compound according to this invention may be given in different dosage forms for administering in any suitable enteral or parenteral way. The dosage forms, like tablets, pills, injection, liquids, and the like, may be manufactured by the known principles in the art. Once can use any pharmaceutically accepted additives, lubricants, fillers, and the like, to modify different properties of the dosage forms.

Catechol-O-methyltransferase (COMT) catalyzes the transfer of the methyl group from S-adenosyl-L-methionine to a number of compounds with catechol structures. This enzyme is important in the extraneuronal inactivation of catecholamines and drugs with catechol structures. COMT is one of the most important enzymes involved in the metabolism of catecholamines. It is present in most tissues, both in the peripheral and the central nervous system. The highest activities are found in the liver, intestine and kidney. COMT probably is present in soluble and membrane bound forms. The exact character of the two forms has not been established.

In Parkinson's disease the dopaminergic neurones, primarily the nigrostriatal neurones, are damaged, causing dopamine deficiency in the cerebral basal ganglia. This deficiency can be compensated by levodopa which is converted to dopamine in the central nervous system under the influence of DDC.

Today, levodopa treatment is almost invariably supplemented with a peripheral DDC inhibitor to inhibit early dopamine formation and thereby increase the cerebral levodopa concentration and decrease the peripheral side effects of dopamine.

In addition to DDC, COMT metabolizes levodopa, converting it 3-0-methyldopa (3-OMD). 3-OMD readily penetrates the blood-brain barrier via an active transport system. Alone it is therapeutically ineffective and detrimental when competing with levodopa. 3-OMD is accumulated in tissues because of its long half-life (about 15 hours) compared to levodopa (about 1 hour). The high activity of COMT clearly correlates with the poor efficacy of levodopa despite the presence of peripheral DDC inhibitor.

In addition to monoamine oxidase (MAO), COMT is a major enzyme participating in the amine metabolism. By inhibiting the metabolism of endogenous amines (dopamine, noradrenaline, adrenaline) in the brain the COMT inhibitors decrease decomposition of these compounds. Thus, they may be useful in the treatment of depression.

By inhibiting peripheral COMT effectively, COMT inhibitors direct the metabolic route of levodopa towards decarboxylation, forming thereby more dopamine which is important in the treatment of hypertension and heart failure.

The COMT inhibitor of the present invention, which inhibits formation of 3-OMD, may decrease the adverse effects of long-term use of levodopa. Furthermore, levodopa doses can be reduced. It has been shown that the dose of levodopa can be reduced by half or to one-third of the dose used without a COMT inhibitor. Since dosage of levodopa is individual, it is difficult to give any absolute dosage, but daily doses as low as 50 to 400 mg have been considered sufficient to start with.

The following example illustrates the invention.

EXAMPLE 1

The crude synthesis product (3.0 kg) prepared according to the method described in British patent application No. 8727854 was dissolved in 8.0 kg of acetic acid (98-100%) (or formic acid) containing 80 g of hydrogen bromide (or 40 g of hydrogen chloride) by heating to 90° C. The solution was slowly cooled to 20° C. and stirred for 20 h at 20° C. and finally for 6 h at 15° C. The crystalline product was filtered and washed carefully first with a cold (4° C.) mixture (1:1) of toluene-acetic acid (1:1 v/v) and then with cold toluene (1:1). The product was dried in vacuum at 45° C. Yield of crystallographically pure A form of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitro-phenyl) acrylamide was 2.4 kg (80%), m.p. 162-163° C.

We claim:

1. The crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4dihydroxy-5-nitrophenyl)acrylamide having the infrared spectrum in potassium bromide having the following absorption bands:

Wave numbers (cm^{-1})	Wave numbers (cm^{-1})
3339	1512
3092	1441
3066	1377
3039	1298
2981	1281
2938	1210
2217	1165
1628	1150
1607	800
1580	779
1544	740

2. A process for preparing crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide having the infrared spectrum in potassium bromide having the following absorption bands:

Wave numbers (cm^{-1})	Wave numbers (cm^{-1})
3339	1512
3092	1441
3066	1377
3039	1298
2981	1281
2938	1210
2217	1165
1628	1150
1607	800
1580	779
1544	740

which comprises crystallization of the crude N,N-diethyl-2-cyano-3-(3,4-dihydroxy -5-nitrophenyl acrylamide from lower aliphatic carboxylic acid containing a catalytic amount of hydrochloric or hydrobromic acid.

3. The process as claimed in claim 2, wherein said lower aliphatic carboxylic acid is acetic acid.

4. The process as claimed in claim 2, wherein said lower aliphatic carboxylic acid is formic acid.

5. A pharmaceutical composition for inhibiting catechol-O-methyl-transferase, said composition comprising a catechol-O-methyl-transferase inhibiting amount of the crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide of claim 1 and a pharmaceutically acceptable carrier.

6. A method for inhibiting catechol-O-methyl -transferase in a patient, said method comprising administering a catechol-O-methyl-transferase inhibiting amount of the crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide of claim 1, to a patient in need of such treatment.

7. A method for the treatment of Parkinson's Disease, said method comprising administering a catechol-O-methyl-transferase inhibiting amount of the crystallographically essentially pure polymorphic form A of (E)-N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide of claim 1; and a sufficient amount of levodopa to treat Parkinson's disease, to a patient in need of such treatment.

8. The method as claimed in claim 7, further comprising administering a sufficient amount of a peripheral decarboxylase inhibitor to inhibit early dopamine formation.

9. The method as claimed in claim 8, wherein said peripheral decarboxylase inhibitor is carbidopa.

10. The method as claimed in claim 8, wherein said peripheral decarboxylase inhibitor is benserazide.

* * * * *

CIVIL COVER SHEET

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

ORION CORPORATION

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) ATTORNEYS (FIRM NAME, ADDRESS AND TELEPHONE NUMBER)
Richard K. Herrmann/Mary B. Matterer
Morris James LLP
500 Delaware Avenue, Suite 1500
Wilmington, DE 19801
302-888-6800

DEFENDANTS

WOCKHARDT USA, INC. and WOCKHARDT LIMITED

COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT _____
(IN U.S. PLAINTIFF CASES ONLY).

ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION (PLACE AN "X" IN ONE BOX ONLY)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (PLACE AN "X" IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT)
(For Diversity Cases Only)

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Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign County	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. ORIGIN (PLACE AN "X" IN ONE BOX ONLY)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

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- ☐ 120 Marine
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- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury Med. Malpractice
- ☐ 365 Personal Injury – Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R. R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt Relations
- ☐ 730 Labor/Mgmt Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS – Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce/ICC Rates/etc.
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 891 Agricultural Arts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes
- ☐ 890 Other Statutory Actions

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence
- HABEAS CORPUS:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE BRIEF STATEMENT OF CAUSE. DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY.)

Action for patent infringement under 35 U.S.C. §§ 271 et seq.

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23 **DEMAND $** CHECK YES only if demanded in complaint: **JURY DEMAND:** ☐ YES ☒ NO

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE DOCKET NUMBER

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September 13, 2007

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RECEIPT# _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

07-550

Civil Action No. _____

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 3 COPIES OF AO FORM 85.

9/13/2007
(Date forms issued)

Susan C. Hadley
(Signature of Party or their Representative)

Susan Hadley
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action